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The Patentability of Genetic Therapies: CAR-T and Medical Treatment Exclusions Around The World

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**THE PATENTABILITY OF GENETIC THERAPIES:
CAR-T AND MEDICAL TREATMENT EXCLUSIONS AROUND THE WORLD**

LUIS GIL ABINADER^{*} AND JORGE L. CONTRERAS^{1**}

Draft: May 15, 2019

ABSTRACT

More than eighty countries, including the members of the European Patent Convention, the United States, Canada, New Zealand, China, Japan, and India, currently exclude or limit the patentability of methods of medical treatment. CAR-T and other recent gene and cell therapies, which operate based on the extraction of genetic or cellular material from a patient, the alteration of such material, and the reintroduction of such material to the patient's body, should, under most or all of these legal regimes, be considered medical treatments that are thus excluded from patentability, or as to which patent enforcement is limited. Accordingly, we urge national patent offices to update their examination procedures and practices to take these patentability limitations into account, and to publish guidance clearly explaining this approach to applicants.

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INTRODUCTION

Recent scientific breakthroughs have enabled the development of a new class of human therapies that harness a patient's own cells to achieve therapeutic results. One of the most promising of these is an immunotherapy that utilizes chimeric antigen receptor T-cells (CAR-T) to enhance a patient's ability to combat tumor cells.² Other promising types of gene therapy can replace a defective copy of a patient's gene with a modified gene that is inserted into the patient's cells.³ Researchers continue to explore stem cell treatments that will make use of regenerative pluripotent stem cells harvested from a patient's body.

While treatments such as these have been discussed for years, it is only recently that regulatory agencies have begun to approve them for use in human patients. In 2017, the U.S. Food and Drug Administration (FDA) approved the first two CAR-T therapies for use in the United States: Novartis's Kymriah (tisagenlecleucel)⁴ and Kite/Gilead's Yescarta (axicabtagene ciloleucel),⁵ both of which are indicated for blood-based cancers (lymphoblastic leukemia and B-cell lymphoma, respectively). European and Canadian approval of these treatments followed in 2018.⁶

While these new therapies have the potential to save and drastically improve human life, their announced prices have also set new records. Kymriah reportedly costs US\$475,000 per treatment,⁷ and Yescarta will be priced at US\$373,000.⁸ And recently Novartis announced that \$4–5 million per patient would be a “cost effective” price for a gene therapy under development for spinal muscular atrophy (SMA).⁹ These high price tags portend a large and highly lucrative market ahead for CAR-T and similar therapies. One market analyst predicts that the global CAR-T market will expand from \$168 million in 2018 to \$8 billion in 2028.¹⁰

Given the high profits anticipated from these novel therapies, it is not surprising that the firms developing them have sought patents covering many aspects of their manufacture, composition, and use.¹¹ However, unlike new small molecule drugs and biologics, these therapies are not novel compounds or biological entities but modified versions of a patient's own cells.¹² As

² See, e.g., Denise Grady, F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing \$475,000, **N.Y. Times** (Aug. 30, 2017), <https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html> (describing the University of Pennsylvania researchers' treatment using the CAR-T cell therapy).

³ Gina Kolata, New Gene-Therapy Treatments Will Carry Whopping Price Tags, **N.Y. Times** (Sept. 11, 2017), <https://www.nytimes.com/2017/09/11/health/cost-gene-therapy-drugs.html>.

⁴ See U.S. Food & Drug Ass'n, **BL 125646/0, Biologics License Application Approval Letter for Novartis Pharmaceuticals 1** (Aug. 30, 2017) [hereinafter **Novartis Approval Letter**].

⁵ See U.S. Food & Drug Ass'n, **BL 125643/0, Biologics License Application Approval Letter for Kite Pharma 1** (Oct. 18, 2017) [hereinafter **Kite Approval Letter**].

⁶ See discussion *infra* Section I.B.3 (discussing regulatory approvals).

⁷ Kolata, *supra* note 2.

⁸ Deena Beasley, U.S. Medicare Sets Outpatient Rate for Yescarta Reimbursement, **Reuters** (Apr. 5, 2018), <https://www.reuters.com/article/us-cancer-medicare-yescarta/u-s-medicare-sets-outpatient-rate-for-yescarta-reimbursement-idUSKCN1HC2N3>.

⁹ John Miller, Novartis Says SMA Gene Therapy is Cost-Effective At \$4-5 Mln Per Patient, **Reuters** (Nov. 5, 2018), <https://www.reuters.com/article/novartis-gene-therapy/novartis-says-sma-gene-therapy-is-cost-effective-at-4-5-mln-per-patient-idUSFWN1XG0OD>.

¹⁰ Jeannie Baumann, Breakthrough Cancer Therapy Stalls in Manufacturing Bottleneck, **Bloomberg Law News**, Feb. 12, 2019.

¹¹ See discussion *infra* Section II (discussing patent coverage).

¹² See Grady, *supra* note 1 (stating that these treatments “turn patient's cells into a ‘living drug’”).

such, one must ask whether therapies such as Kymriah and Yescarta are drugs, as their manufacturers characterize them, or methods of medical treatment. The distinction is a crucial one, as the laws of more than eighty countries around the world prohibit the patenting of methods of medical treatment, and even countries such as the United States, Canada, and Australia, which do not expressly prohibit such patents, may significantly limit the scope of patenting and enforcement.¹³

In this article we ask whether therapies that act primarily to alter a patient's own cells, particularly CAR-T therapies such as Kymriah and Yescarta, should be considered methods of medical treatment that are largely ineligible for patent protection around the world and, if so, how national patent offices, legislatures, and courts should respond.¹⁴ The remainder of this article proceeds in four principal Parts as follows: Part I provides an overview of the scientific and regulatory background of CAR-T and other gene and cell therapies such as Kymriah and Yescarta. Part II describes the patenting exclusion for methods of medical treatment around the world. Part III analyzes the degree to which CAR-T and other gene and cell therapies should be considered methods of medical treatment that are ineligible for patent protection, or subject to limitations on patent protection. And Part IV considers the implications of the potential loss of patentability on the development and market for such therapies, as well as potential governmental reactions.

I. CAR-T AND GENETIC THERAPIES

While a number of different therapy types make use of a patient's cells, we focus in this article on CAR-T therapies, both because they present a clear case for characterization as therapeutic methods and because there are multiple CAR-T therapies that have received regulatory approval and are now being administered to human patients.¹⁵

A. Overview of CAR-T Therapy

Broadly speaking, CAR-T therapies involve the modification of a patient's T-lymphocytes (white blood cells that play a key role in the immune system) so as to target particular forms of tumor cells.¹⁶ An overview of the CAR-T treatment process is illustrated in Fig. 1 (note its characterization as a "cell manufacturing" process by the vendor).

¹³ See Paul Mazzola, Primer on Patenting Methods of Medical Treatment in the United States and Abroad, *Healio* (Aug. 4, 2017), <https://www.healio.com/orthopedics/business-of-orthopedics/news/online/%7B9b2e4d7f-e2b1-4be9-a728-7bccf1dc0a3b%7D/primer-on-patenting-methods-of-medical-treatment-in-the-united-states-and-abroad> (highlighting Australia, Canada, and Europe's patentability limitations on methods of human therapy treatments).

¹⁴ But see Jacob S. Sherkow, Patricia J. Zettler, and Henry T. Greely, *Is It 'Gene Therapy'?*, *J.L. Biosci.* (2018) ("all therapies, in some sense, affect a patient's genes, whether it's through altering transcription, regulating translation, or even modifying the epigenome. A relaxing vacation—sun, surf, and sangria—arguably does more to regulate gene expression than many 'precision' therapies").

¹⁵ See, e.g., NCI Staff, With Federal Approval for Advanced Lymphoma, Second CAR T-Cell Therapy Moves to the Clinic, *Nat'l Cancer Inst.* (Oct. 25, 2017), <https://www.cancer.gov/news-events/cancer-currents-blog/2017/yescarta-fda-lymphoma> (stating that the Food and Drug Administration approved the use of "axicabtagene ciloleucel (Yescarta™)" in treating patients with large-B-cell lymphomas).

¹⁶ See *id.*

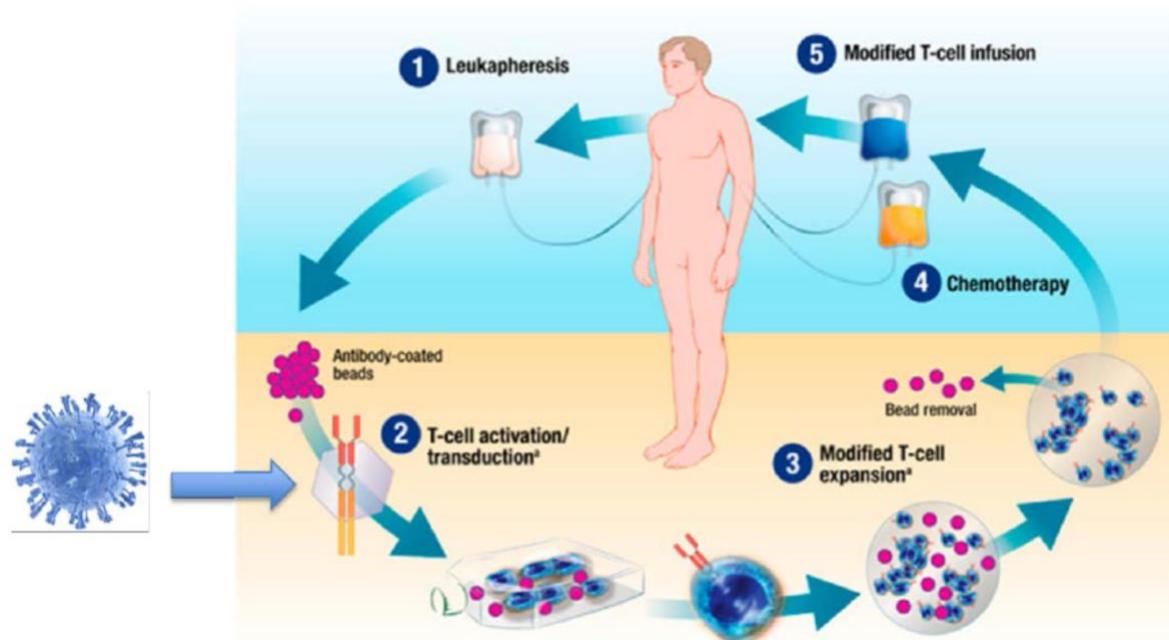


Figure 1 – Overview of CAR-T cell manufacturing process¹⁷

As shown in Figure 1, the first stage of CAR-T treatment is the extraction of T-cells from a patient's body through a procedure known as leukapheresis.¹⁸ While leukapheresis is performed on site at the patient's healthcare facility, extracted cells are sent to a centralized laboratory (in the case of Kymriah, a Novartis's facility in either Morris Plains, New Jersey or Fraunhofer, Germany).¹⁹ Because leukapheresis collects multiple cell types in a mixture that may vary based on the patient's disease stage, genetics, age, and treatment history, the collected cellular material must be processed to reduce these impurities.²⁰ If insufficient T-cells remain, T-cell enrichment steps may be necessary.²¹

Once the patient's T-cells are collected and processed, they are treated with synthetic antigen receptors (CARs) that are known to bind to particular proteins expressed on the surface of tumor cells.²² In the case of Kymriah, the target protein is known as CD19, which is expressed on the surface of B cell tumors.²³ A retroviral vector then introduces the synthetic CAR to the patient's T-cells.²⁴ In some cases, the vector may be inserted into the T-cell using a gene editing technique

¹⁷ U.S. Food & Drug Ass'n, BLA 125646, FDA Briefing Document for Tisagenlecleucel, Novartis Pharmaceuticals 14 (2017) [hereinafter Novartis FDA Briefing].

¹⁸ *Id.* at 18.

¹⁹ *See id.* at 43.

²⁰ *See id.* at 18.

²¹ *Id.*

²² *Id.* at 14. *See generally* Carl H. June & Michael Sadelain, *Chimeric Antigen Receptor Therapy*, 379 *N. Eng. J. Med.* 64 (2018) (providing an overview of the technology).

²³ *Id.* at 16.

²⁴ *See id.* at 17; *see also* Justin Eyquem et al., *Targeting a CAR to the TRAC Locus with CRISPR/Cas9 Enhances Tumour Rejection*, 543 *Nature* 113, 113 (2017).

such as CRISPR-Cas9.²⁵ The modified T-cells, which the manufacturer refers to as its “product,” are then reintroduced to the patient’s bloodstream at the healthcare facility.²⁶

In the patient’s body, the modified T-cells are attracted to tumor cells by means of their new antigen receptors.²⁷ Once a modified T-cell comes into proximity with a tumor cell, it attacks the tumor by releasing toxic granules (cytotoxicity) or by signaling other cells to attack the tumor (cytokine signaling).²⁸ These mechanisms are illustrated in Fig. 2 and have proven to be clinically efficacious.²⁹ Novartis reported a complete remission rate of 82.5% six months after Kymriah was administered in a Phase II single-arm multicenter trial in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia.³⁰

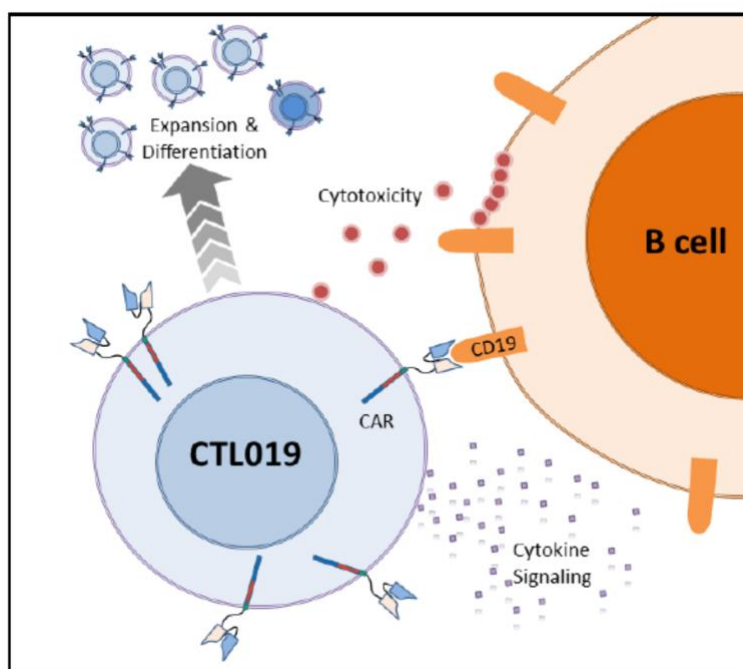


Figure 2 – Tisagenlecleucel mechanisms of action³¹

²⁵ Eyquem et al., *supra* note 22, at 113.

²⁶ Novartis FDA Briefing, *supra* note 17, at 1, 8, 9.

²⁷ *Id.* at 17.

²⁸ *Id.* at 17–18.

²⁹ *Id.* at 15.

³⁰ *Id.* at 8.

³¹ Novartis FDA Briefing, *supra* note 17, at 15.

B. Regulatory Approval of Gene and Cell Therapies

1. U.S. Regulatory Framework for Gene Therapies

In the United States, gene and cell therapies are regulated as biological products, or biologics, under the Public Health Service Act (PHSA)³² and the Federal Food, Drug, and Cosmetic Act (FDCA).³³ An applicant seeking approval to market and distribute a new biologic in the United States must complete preclinical laboratory tests, animal studies, and formulation studies as well as human clinical trials to establish the safety, potency, and purity of the product candidate for each proposed indication.³⁴

In addition, the FDA defines a “gene therapy product” as a product that operates by transcription and/or translation of transferred genetic material and/or by integrating into the host genome, and which is administered using nucleic acids, viruses, or genetically engineered microorganisms.³⁵ Gene therapy products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient.³⁶ The FDA and the NIH have published guidance documents with respect to the development and submission of protocols for gene therapy products that provide additional factors that the FDA will consider at each stage of development.³⁷

In order to obtain marketing approval for a new gene therapy product, an applicant must submit a Biologics License Application (BLA) to the FDA requesting marketing approval for one or more proposed indications, including detailed information on the manufacture and composition of the product and its proposed labeling.³⁸ The BLA must contain extensive manufacturing information and detailed information on the composition of the product and its proposed labeling.³⁹

As part of its BLA review, the FDA will inspect the manufacturing facilities at which the proposed product and its components will be produced to assess compliance with the FDA’s current Good Manufacturing Practices (cGMP) requirements and to assure that the facilities, methods, and controls are adequate to preserve the product’s identity, strength, quality, and purity.⁴⁰ In addition, when human cellular and tissue products are involved, the FDA will assess the applicant’s compliance with the FDA’s Current Good Tissue Practices (CGTP), which seek to

³² See Public Health Service Act, 42 U.S.C. § 262 (2017) (establishing the procedures for the issuance of biologics licenses).

³³ See Federal Food, Drug, & Cosmetic Act, 21 U.S.C. § 301 (2017) (authorizing the FDA to generally oversee the safety of food, drugs, medical devices, and cosmetics in the United States).

³⁴ U.S. Food & Drug Ass’n, **Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)** 1–2 (2018) [hereinafter **INDs Information**] (“This guidance applies to human gene therapy products and to combination products that contain a human gene therapy in combination with a drug or device.”).

³⁵ U.S. Food & Drug Ass’n, **Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events** 4 (2006) [hereinafter **FDA Gene Therapy Guidance**] (defining gene therapy products as “[a]ll products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms”). See generally Sherkow et al, *supra* note 16 (overview of FDA’s attempts to define “gene therapy”).

³⁶ *Id.*

³⁷ See *id.* at 8.

³⁸ 21 C.F.R. § 601.2(a) (2018).

³⁹ *Id.*

⁴⁰ *Id.* § 606.40.

ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission, and spread of communicable disease.⁴¹

The FDA may approve a BLA if it determines that the proposed biologic product is safe, pure, and potent and the facility where the product will be manufactured meets all required standards.⁴² Upon approval of a BLA, the FDA may issue an approval letter or a complete response letter.⁴³ An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications.⁴⁴ If the application is not approved, the FDA will issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application.⁴⁵

2. EU Regulatory Framework for Gene Therapies

The process governing approval of medicinal products in the European Union is similar to that in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication.⁴⁶ In order to receive marketing approval for a new product in the EU, an applicant must submit a marketing authorization application (MAA) under a centralized procedure administered by the European Medicines Agency (EMA).⁴⁷

The marketing of products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation (EC) No 1394/2007 on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products.⁴⁸ Regulation (EC) No 1394/2007 establishes specific rules concerning the authorization, supervision, and pharmacovigilance of “gene therapy medicinal products”, “somatic cell therapy medicinal products”, and “tissue engineered products”.⁴⁹ Manufacturers of such advanced therapy “medicinal products” must demonstrate their quality, safety, and efficacy to EMA, which renders an opinion regarding the application for marketing authorization.⁵⁰ The European Commission then grants or refuses marketing authorization in light of the opinion delivered by EMA.⁵¹ We note however that the characterization of gene and cell therapies as a “product”, as the in the Directive 2001/83/EC which uses phrases such as “somatic cell therapy medicinal products”, is largely a fiction. Here the “product” in question is a batch of the patient’s own cells that are taken from the

⁴¹ U.S. Food & Drug Ass’n, **Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS)** 3 (2011) [hereinafter **FDA Good Tissue Practice Guidance**].

⁴² § 610.9(a)-(b) (outlining the requirements for the modification of a test method or manufacturing process).

⁴³ 21 C.F.R. § 601.3(a) (2018).

⁴⁴ <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page> (last accessed Mar. 30, 2019).

⁴⁵ § 601.3(a)(2).

⁴⁶ Council Regulation 2017/745, 2017 O.J. (L 117) 1, 1–2 (EU).

⁴⁷ *Id.* at 2, 13 (“[T]he Commission should ensure an appropriate level of consultation of the European Medicines Agency (EMA), the European Chemicals Agency and the European Food Safety Authority.”).

⁴⁸ Council Regulation 1394/2007, 2007 O.J. (L 324) 121 (EC); Council Directive 2001/83/EC, 2001 O.J. (L 311) 67 (EC).

⁴⁹ Council Regulation 1394/2007, *supra* note 45, at 121.

⁵⁰ *Id.* at 122, 124.

⁵¹ *Id.*

patient, altered, and then re-introduced into the patient's body. We discuss this further in Part III.B, below.

3. Recent CAR-T Regulatory Approvals

The first applicant to seek U.S. regulatory marketing approval for a CAR-T candidate therapy appears to have been Juno Therapeutics, a leader in CAR-T research.⁵² Juno's JCAR015 therapy was jointly developed with Cellgene and targeted Adult B-cell acute lymphoblastic leukemia (ALL).⁵³ But despite early promise, the FDA halted Juno's JCAR015 Phase II trial in March 2017 after five patient deaths resulting from cerebral edema.⁵⁴ Juno is reportedly in clinical trials for one or more additional CAR-T based therapies.⁵⁵

Novartis received U.S. market approval for Kymriah (tisagenlecleucel) on August 30, 2017.⁵⁶ This approval authorizes Kymriah as "a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse."⁵⁷ Because of the pediatric indication for which Kymriah was approved, Novartis also received a transferable, salable "rare pediatric disease priority review voucher" under Section 529 of the Food, Drug, & Cosmetic Act.⁵⁸ Because the indication for which Kymriah's market approval was sought affects fewer than 200,000 individuals in the U.S., Novartis was also granted "orphan drug" status for Kymriah.⁵⁹

Novartis received market approval for Kymriah in the EU on August 27, 2018.⁶⁰ This approval authorizes the marketing of Kymriah in the EU for two indications: the treatment of B cell ALL that is refractory, in relapse post-transplant or in second or later relapse in patients up to 25 years of age; and the treatment of relapsed or refractory diffuse large B cell lymphoma

⁵² Alex Lash, *After Trial Deaths, Juno Pivots and Scraps Lead CAR-T Therapy*, *Xconomy* (Mar. 1, 2017), <https://xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/>.

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ **Novartis Approval Letter**, *supra* note 3, at 1.

⁵⁷ *Id.*

⁵⁸ *Id.* at 4.

⁵⁹ **Novartis Approval Letter**, *supra* note 3, at 5. Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for rare diseases or conditions (i.e., conditions that affect fewer than 200,000 individuals in the United States or that affect more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the product will be recovered from U.S. sales of the product). An orphan drug designation granted by the FDA confers on the sponsor a seven-year market exclusivity. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market a product. See *Developing Orphan Products: FDA and Rare Disease Day*, **FDA** (2011), <https://www.fda.gov/forindustry/Developingproductsforrareconditions/ucm239698.htm>.

⁶⁰ Summary of European Union Decisions on Marketing Authorization in Respect of Medicinal Products from 1 August 2018 to 31 August 2018, 2018 O.J. (C 349) 1, 2 (EC).

(DLBCL) after two or more lines of systemic therapy in adult patients.⁶¹ Kymriah also received orphan market exclusivity in Europe.⁶²

Novartis obtained approval for Kymriah in Canada on September 5, 2018.⁶³ The authorization by Health Canada covers the following indication: treatment of pediatric and young adult patients 3 to 25 years with B-cell ALL who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.⁶⁴

Kite Pharma received U.S. market approval history for Yescarta (axicabtagene ciloleucel) on October 18, 2017.⁶⁵ This approval authorizes Yescarta “for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.”⁶⁶

Kite Pharma received market approval for Yescarta in the EU on August 27, 2018.⁶⁷ This approval grants Yescarta an orphan market exclusivity that is due to expire on August 27, 2028.⁶⁸ In the EU Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.⁶⁹

Most recently, CRISPR Therapeutics has received FDA approval for an investigational new drug application for its CTX001 CAR-T therapy targeting beta thalassemia and sickle cell disease.⁷⁰

⁶¹ See Product Information (Kymriah), Eur. Comm’n: Public Health, <http://ec.europa.eu/health/documents/community-register/html/h1297.htm>. (last visited Feb. 18, 2019) (explaining the parameters for authorized marketing of Kymriah).

⁶² See id. EC Regulations No. 141/2000 and No. 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish that the product is intended for the diagnosis, prevention, or treatment of (i) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU, or (ii) a life-threatening, seriously debilitating, or serious and chronic condition in the EU that, without additional incentives, is unlikely to generate sufficient returns to justify the investment necessary to produce and market the product. In each of these cases, the applicant must demonstrate that no authorized method of diagnosis, prevention, or treatment of the condition in question exists or, if such method exists, the product will be of significant benefit to those affected by the relevant condition. Marketing authorization for an orphan drug confers a ten-year period of market exclusivity (which may be reduced to six years if, at the end of the fifth year, the product no longer meets the criteria for orphan drug designation). See Council Regulation 141/2000, 2000 O.J. (L 18) 1, 4–5 (EC); Commission Regulation 847/2000, 2000 O.J. (L 103) 1, 5 (EC).

⁶³ Regulatory Decision Summary – Kymriah – Health Canada, Gov. Can.: Health Product Reg., <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00423> (last visited Feb. 18, 2019).

⁶⁴ Regulatory Decision Summary – Kymriah – Health Canada, supra note 60.

⁶⁵ See Kite Approval Letter, supra note 4.

⁶⁶ Id.

⁶⁷ Summary of European Union Decisions on Marketing Authorization in Respect of Medicinal Products from 1 August 2018 to 31 August 2018, supra note 57, at 2.

⁶⁸ Product Information (Yescarta), Eur. Comm’n: Pub. Health, <http://ec.europa.eu/health/documents/community-register/html/h1299.htm#EndOfPage> (last visited Feb. 18, 2019).

⁶⁹ Id.

⁷⁰ Bailey Lipschultz, *Crispr Got FDA Nod for Another Gene Editing Study, Dosing Next*, Bloomberg Law News, Apr. 29, 2019.

Beyond this, many more CAR-T and other gene and cell therapy are likely to seek regulatory approval in the near future. One commentator reports that in February 2019, there were nearly 700 CAR-T studies registered in the NIH's ClinicalTrials.gov database.⁷¹

C. The Patenting of CAR-T

As with many new biomedical developments, the firms bringing CAR-T treatments to market have acquired patents covering many aspects of these treatments. One of the first U.S. patents covering CAR-T technology is entitled “Nucleic Acids Encoding Chimeric T Cell Receptors” and was issued in 2008 to the Sloan-Kettering Institute for Cancer Research in New York.⁷² The thirteen claims of this patent (one independent and twelve dependent) claim various configurations of a “nucleic acid polymer encoding a chimeric T cell receptor”—a composition of matter.⁷³ This patent, in turn, has been cited by ninety-seven later patents and patent applications.⁷⁴ As discussed below, many of these later patents and applications claim not only compositions of matter, but methods of treating various diseases using CAR-T technologies.⁷⁵

In April 2019, Björn Jürgens and Nigel Clarke published a study of CAR-T patenting commissioned by the European Patent Office (EPO).⁷⁶ Jürgens and Clarke report that the patenting of CAR-T inventions began in earnest in 2013 with sixty filings around the world and increased through 2016 to 597 filings.⁷⁷ Of a total of 1,914 patent documents filed between 2013 and 2016, the greatest number were filed by applicants originating in the U.S. (39%) and China (33%), followed by the UK (5%), Germany (5%), Japan (4%) and France (3%).⁷⁸ The jurisdictions in which patent documents were filed included the U.S. (approximately 380 documents), the EPC (approximately 190 documents), Australia (approximately 160 documents) and Canada (approximately 130 documents).⁷⁹

The authors conducted a further analysis of CAR-T patent filings. Table 1 shows the results of a search in the USPTO patent database for issued patents and published patent applications containing the term “chimeric antigen receptor” either in all of the search fields, in their abstracts, or in their claims.⁸⁰

⁷¹ Baumann, *supra* note 12.

⁷² See U.S. Patent No. 7,446,190 B2 (filed May 28, 2003) (issued Nov. 4, 2008) (featuring the full patent for Nucleic Acids Encoding Chimeric T Cell Receptors).

⁷³ *Id.* (“This application relates to nucleic acid polymers encoding chimeric T cell receptors. . .”).

⁷⁴ See Nucleic Acids Encoding Chimeric T Cell Receptors, **Google Patents**, <https://patents.google.com/patent/US7446190B2/en?q=7%2c446%2c190> (search “Pat. No. 7,446,190” then scroll down to “cited by”) (last visited Feb. 18, 2019) (providing a list of all publications that have cited to Pat. No. 7,446,190).

⁷⁵ See discussion *infra* Part X.

⁷⁶ Björn Jürgens & Nigel Clarke, Evolution of CAR T-cell immunotherapy in terms of patenting activity, 37 *Nature Biotechnology* 230 (2019).

⁷⁷ *Id.* at 371.

⁷⁸ *Id.* at 372.

⁷⁹ *Id.*

⁸⁰ See Chimeric Antigen Receptor, **U.S. Pat. and Trademark Off.**, <http://patft.uspto.gov/netahtml/PTO/search-bool.html> (search “Chimeric Antigen Receptor” then adjust dates) (last visited Feb. 20, 2019); see also Chimeric Antigen Receptor, **U.S. Pat. and Trademark Off.**, <http://appft.uspto.gov/netahtml/PTO/search-bool.html> (search “Chimeric Antigen Receptor”) (last visited Feb. 20, 2019). This search strategy is consistent with that of Jürgens & Clarke, *supra* note 75, at Supp.

Table 1

*U.S. issued patents and patent applications citing “chimeric antigen receptor”, by year*⁸¹

Year	Issued patents			Published applications		
	All fields	Abstract	Claims	All fields	Abstract	Claims
2011	0	0	0	6	0	0
2012	0	0	0	12	1	7
2013	4	0	2	32	3	15
2014	10	1	6	65	20	38
2015	27	1	12	104	14	45
2016	64	8	24	239	35	123
2017	117	15	41	455	67	200
2018	195	14	57	730	103	327

Table 1 is not intended to be a comprehensive landscape of CAR T patenting activity in the U.S.⁸² Although the fact that a patent document mentions the phrase “chimeric antigen receptor” in the description or any other field is indicative, this does not necessarily mean that it is claiming a CAR T therapy. Conversely, CAR T therapies may be claimed in patent documents without using the phrase “chimeric antigen receptor,” and such patent documents are not included in the search strategy described in Table 1. For instance, as of March 2019, there are three issued patents in the U.S. that use the phrase “synthetic T-cells” but do not mention the phrase “chimeric antigen receptor”; similarly, there is one issued patent in the U.S. citing “CAR-modified T-cells” that does not mention “chimeric antigen receptor.” Nevertheless, Table 1 provides an easily-replicable illustration of the growth in patents and applications mentioning “chimeric antigen receptor.”

In Europe, the number of CAR-T patents appears to be lower. An Espacenet search for B1, B2, or B3 documents (codes used to identify granted patents) citing the phrase “chimeric antigen receptor” in the title or abstract only returns nine European patents.⁸³ Two of those patents claimed methods where one of the steps involves administering T cells to a patient.⁸⁴

⁸¹ *Id.*

⁸² For patent landscaping guidelines in the life sciences, see e.g., Tania Bubela, E Richard Gold, Gregory D Graff, Daniel R Cahoy, Dianne Nicol and David Castle. *Patent landscaping for life sciences innovation: toward consistent and transparent practices*. 31 *Nature Biotechnology* 202 (2013); Mateo Aboy, Kathy Liddell, Johnathon Liddicoat, and Cristina Crespo. *Myriad's Impact on Gene Patents*. 34 *Nature Biotechnology*, 1119 (2016).

⁸³ See *Espacenet Patent Search*, *Eur. Pat. Off.*, <https://worldwide.espacenet.com> (last visited Feb. 16, 2019) (listing all patents within this search, including those from countries outside of Europe).

⁸⁴ See *id.*

A PatentScope search⁸⁵ for applications that include any of the following phrases: "administering to a patient," "administering to a subject," "administering to said subject," and "administering to said patient," conducted in October 2018, returned a total of eighty-three patent applications filed at the EPO. A review of these eighty-three applications using the European Patent Register online legal status database⁸⁶ reflects that as of December 2018, seventy-five of those applications were still pending,⁸⁷ and six have been withdrawn. The EPO has expressed its intent to grant only two of those eighty-three applications; in both of those applications the claims with the term "administering [...]" were abandoned, eliminated during examination, or were not introduced at the EPO despite being present in the priority application.⁸⁸ These figures are lower than those reported by Jürgens & Clarke, most likely due to the more restrictive search terms that we employed.

II. PATENT EXCLUSIONS FOR METHODS OF MEDICAL TREATMENT

A. *Background: Nineteenth and Early Twentieth Centuries*

Since the early days of patenting there has been unease with regard to granting particular inventors exclusive rights over methods of medical treatment. Objections to the patenting of medical treatments have their roots in basic moral principles—it is wrong to limit the availability of potential lifesaving treatments to individuals in need—as well as ethical precepts of the medical profession.⁸⁹ That is, in keeping with the Hippocratic Oath, it was argued that “in order to ensure the best possible health treatment, physicians must always be free in their choice of treatment.”⁹⁰ Thus, when the American Medical Association adopted its first Code of Ethics in 1847, its members agreed that obtaining a patent on a medical procedure was “derogatory to professional character.”⁹¹

⁸⁵ See **Word Intell. Prop. Org.: Patentscope**, <https://patentscope.wipo.int/search/en/search.jsf> (last visited Feb. 16, 2019) (providing the complete results of the aforementioned search).

⁸⁶ **European Patent Register, Eur. Pat. Off.**, <https://register.epo.org/regviewer> (last visited Feb. 16, 2019).

⁸⁷ *Id.* In the context of this paper pending means that a published application has not yet been issued, rejected, or withdrawn. At the European Patent Register database, the legal status of pending applications could be coded in several ways, including as “the application has been published”, “request for examination was made”, “examination is in progress.”

⁸⁸ **European Patent Register**, *supra* note 76.

⁸⁹ O. Mitnovetski & D. Nicol, *Are Patents for Methods of Medical Treatment Contrary to the Ordre Public and Morality or “Generally Inconvenient”?*, 30 **J. Med. Ethics** 470, 470 (2004) (“Medical law has its origins in the Hippocratic Oath, and the goal is the preservation of human life. Since the goal of patent law is to encourage innovation by rewarding inventors, it is quite distinct from the goal of medical law.”).

⁹⁰ *Id.*

⁹¹ See Katherine J. Strandburg, *Derogatory to Professional Character? The Evolution of Physician Anti-Patenting Norms, in Creativity Without Law: Challenging the Assumptions of Intellectual Property* 63, 63 (K. Darling & A. Perzanowski eds., 2017) [hereinafter Strandburg, *Derogatory to Professional Character?*]; see also Katherine J. Strandburg, *Legal But Unacceptable: Pallin v. Singer and Physician Patenting Norms, in Intellectual Property at the Edge* 321, 323 (Rochelle Dreyfuss & Jane Ginsburg eds., 2014) [hereinafter Strandburg, *Legal But Unacceptable*] (specifying that the first Code of Ethics in 1847 found it to be unethical for a physician to hold a patent). In the early years of the twentieth century, a similar aversion to the patenting of drugs can be found. See **Joseph Gabriel, Medical Monopoly** (2014).

Patent offices and courts around the world generally agreed with the assessment of the medical community and effectively prohibited patents on methods of medical treatment through the nineteenth and early twentieth centuries.⁹² Accordingly, patents were denied or invalidated in the United States for the use of ether as a surgical anesthetic⁹³ and for the treatment of skin infections using light rays.⁹⁴ Patents were also denied in the United Kingdom for a process for extracting toxic lead from a patient,⁹⁵ and in Germany for the therapeutic administration of oxygen through a hydrogen peroxide bath.⁹⁶ In many of these cases, particularly in Europe, courts reasoned that a patent could not be issued for a process that failed to result in a “vendible product”—something that could be sold.⁹⁷ France and Italy adopted a test of “industrial character” for the issuance of patents on medical innovations,⁹⁸ and Austria and Switzerland based the refusal of such patents on ethical grounds.⁹⁹

Yet despite these early inclinations against patenting medical treatments, the tide began to shift during the 1950s. One watershed occurred in 1954, when the U.S. Patent and Trademark Office expressly overturned an 1883 decision prohibiting the patenting of medical procedures.¹⁰⁰ In 1959 the Australian High Court ruled that a method need not result in a “vendible product” in order to be patentable, expressly departing from the earlier rule expressed in the UK.¹⁰¹ These events, and the increase in patenting activity that followed, contributed to renewed interest in medical treatment patents around the world.

⁹² See Strandburg, *Legal but Unacceptable*, *supra* note 81, at 321–23 (outlining the early history of the medical community’s attitude towards medical patents); see also Mitnovetski & Nicol, *supra* note 79, at 471–72 (tracing the history in the UK and Europe of excluding medical treatments from patenting).

⁹³ *Morton v. New York Eye Infirmary*, 17 F. Cas. 879, 884 (C.C.S.D.N.Y. 1862) (No. 9865); see Strandburg, *Derogatory to Professional Character?*, *supra* note 81, at 64–74 (describing the ether patenting controversy).

⁹⁴ See *Ex Parte Brinkerhoff*, 24 Dec. Comm’r 349 (1883), reprinted in *New Decisions*, 27 *J. Pat. & Trademark Off. Soc’y* 793, 798 (1945) (discussing a patent on “treating animal tissues by subjecting the same to the action of light rays lying within a certain region of the spectrum, the tissues being shielded from wave lengths lying within other regions of the spectrum”).

⁹⁵ *In the Matter of C. & W.’s Application for a Patent*, 31 RPC 235, 235–36 (1914).

⁹⁶ *Badewasser Patent*, Dec. 30, 1904, *Blatt für Patent-, Muster- und Zeichenwesen* [BlfPMZ], vol. 11, no. 1, at 4–5 (Jan. 25, 1905) (Ger.), <https://babel.hathitrust.org/cgi/pt?id=mdp.35112104213360;view=1up;seq=25>.

But see Reiner Moufang, *Methods of Medical Treatment Under Patent Law*, 24 *Intern. Rev. Ind. Prop. & Copyright L.* 18, 22 note 13 (1993) (listing a handful of early German patents issued on medical methods, but never challenged in court, e.g., German patent No. 150666 (1903) for a method of removing stitches from wounds, and German patent No. 150699 (1903) for treating human spinal curvature).

⁹⁷ Mitnovetski & Nicol, *supra* note 79, at 471 (“[I]t [has been] accepted as axiomatic that there [can] be no patents for medical treatment, because they do not result in . . . a product that can be sold.”).

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ See *Ex parte Scherer*, 103 U.S.P.Q (BNA) 107, 110 (Pat. Off. Bd. App. 1954) (stating, in regards to *Morton*, “[i]t is believed that no proper inference that any and all medical or surgical methods are excluded from the field of patentable subject matter can be drawn from the opinion, and neither do the facts upon which the opinion is based warrant such a broad generalization.”); see also Strandburg, *Derogatory to Professional Character? The Evolution of Physician Anti-Patenting Norms*, *supra* note 81, at 76; William D. Noonan, *Patenting Medical and Surgical Procedures*, 77 *J. Pat. & Trademark Off. Soc’y* 651, 655 (1995) (adding that, in 1948, the American Medical Association Judicial Council issued an Official Opinion stating that is no longer considered medical patents to be necessarily unethical).

¹⁰¹ See *Nat’l Research Dev. Corp. v. Comm’r of Patents*, (1959) 102 CLR 252, 253 (Austl.) (holding that the product was patentable because “it consist[ed] in an artificially created state of affairs . . . [a]nd the significance of the product is economic; for it provides a remarkable advantage”); see also Mitnovetski & Nicol, *supra* note 79, at 471.

B. The Methods of Treatment Exclusion Under the European Patent Convention

The European Patent Convention (EPC) is a multilateral treaty among thirty-eight European signatory states representing both members and non-members of the European Union.¹⁰² It establishes a system whereby patent applications may be filed and examined for patentability by a common agency, the European Patent Office (EPO) based in Munich, and then issued as national patents in each of the signatory states (subject to translation and other procedural requirements).¹⁰³

Negotiations and planning for the EPC began as early as 1949 and, in various fits and starts, evolved through numerous stages.¹⁰⁴ By 1969, a first draft of the EPC was developed which listed numerous exclusions from patentability, including “methods of treatments, including methods of diagnosis.”¹⁰⁵

There was debate throughout the negotiation of the EPC whether this exclusion from patentability was based on the notion that patents on medical treatments were contrary to ordre public and morality¹⁰⁶ or because, as argued by the German delegation, such patents were not “susceptible of industrial application”¹⁰⁷ (i.e., harkening back to the UK’s original assessment of such patents as failing to result in vendible products). By the signing of the EPC in 1973, the German view prevailed, and Article 52[4] provided that

Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application . . . This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.¹⁰⁸

¹⁰² Convention on the Grant of European Patents, Oct. 5, 1973, 1065 U.N.T.S. 199 (entered into force Oct. 7, 1977), as amended by the Act revising the Convention on the Grant of European Patents of Nov. 29, 2000 (entered into force Dec. 13, 2007) [hereinafter EPC].

¹⁰³ See *id.* (explaining the process and requirements for obtaining a patent in Europe).

¹⁰⁴ See **Sigrid Sterckx & Julian Cockbain, Exclusions from Patentability: How Far Has the European Patent Office Eroded Boundaries?** 21–39 (Cambridge Univ. Press ed. 2012) (outlining the historical development of the EPC).

¹⁰⁵ EPC, First Preliminary Draft of a Convention Establishing a European System for the Grant of Patents, art. 9(2)(e) (1970) [hereinafter EPC, First Preliminary Draft of a Convention Establishing a European System for the Grant of Patents]. The debates over the EPC were extensive and lengthy. In terms of exclusions from patentability, topics such as the patentability of computer programs, mental processes, and mathematical formulae were particularly contentious. See **Sterckx & Cockbain**, *supra* note 95, at 40–45.

¹⁰⁶ See **Sterckx & Cockbain**, *supra* note 95, at 23 (quoting Roger Gajac’s 1955 study on substantive points of patentability; see also Mitnovetski & Nicol, *supra* note 79, at 470, 472 (explaining that the concept of ordre public “expresses concerns about matters threatening the social structures which tie a society together”). Among the technologies expressly viewed as contrary to the ordre public by the EPO are anti-personnel mines. See **Sterckx & Cockbain**, *supra* note 95, at 57 (providing that at EPC 1973, attendees were told that the EPO believed that inventions “relating to anti-personnel mines *per se* should be excluded from patentability as contrary to ‘ordre public’ and morality”).

¹⁰⁷ See **Sterckx & Cockbain**, *supra* note 95, at 46–47 (asserting that the German view that medical methods are not susceptible of industrial application is a “legal fiction”).

¹⁰⁸ EPC art. 52(4), *supra* note 93.

The EPC entered into effect in July 1978, and the signatory states soon amended their national patent laws to conform to its requirements.¹⁰⁹ Not all countries, however, adopted the “industrial application” language justifying the exclusion of medical treatments from patentability. Denmark, Italy, and Sweden, for example, treated medical treatments as non-inventions, and Switzerland simply characterized them as legal exceptions to patentable subject matter.¹¹⁰

Dissatisfaction with the EPC arose soon after its adoption, and negotiations began for its amendment.¹¹¹ These negotiations were influenced,¹¹² among other things, by the negotiation and ratification of the TRIPS Agreement as part of the World Trade Organization Treaty in 1994¹¹³ and the adoption by the EU of the European Biotechnology Directive of 1998.¹¹⁴ As part of this debate, the “fiction” that certain technologies such as medical treatments lacked industrial application came under fire, largely as part of the larger debate over the patentability of computer software.¹¹⁵

As a result, in the major amendments to the EPC adopted in 2000, which came into force in 2007, the exclusion for medical treatments was moved from Article 52, which permitted patents to be granted on all inventions “susceptible of industrial application,” to Article 53, which included exceptions for inventions “the commercial exploitation of which would be contrary to 'ordre public' or morality.”¹¹⁶ In this manner, the idea that medical treatments lacked industrial application was dispensed with, and it was accepted that the medical treatment exclusion was intended to serve “the interests of public health.”¹¹⁷ The final text of the EPC exclusion for medical treatments, as it exists today, thus reads:

Article 53 – Exceptions to Patentability

European patents shall not be granted in respect of . . . methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.¹¹⁸

The EPO Boards of Appeal have subsequently confirmed that the exclusion of methods of medical treatment from patentability is “based on social-ethical and public health considerations”¹¹⁹ and that “physicians should be free to choose the best medical treatment for a

¹⁰⁹ Mitnovetski & Nicol, *supra* note 79, at 471–72 (“Shortly after signing the EPC, the member states began adjusting their legal systems to accord with European uniform law, and article 52(4) was largely adopted.”).

¹¹⁰ *Id.* at 471.

¹¹¹ See **Sterckx & Cockbain**, *supra* note 95, at 49–65 (tracing the amendments to the EPC, which were born out of dissatisfaction with the original convention).

¹¹² See *id.* at 50–59.

¹¹³ Agreement on Trade-Related Aspects of Intellectual Property Rights, Including Trade in Counterfeit Goods, Apr. 15, 1994, 1869 U.N.T.S. 299, 33 I.L.M. 881 [hereinafter TRIPS Agreement]. See discussion *infra* Part II.B (discussing the medical treatments exclusion under TRIPS).

¹¹⁴ Council Directive 98/44/EC, 1998 O.J. (L 213) 13 (EC).

¹¹⁵ See **Sterckx & Cockbain**, *supra* note 95, at 62–65 (outlining various delegations that criticized this idea).

¹¹⁶ See *id.* at 64–66. These amendments were, in part, enacted to bring the EPC into compliance with the TRIPS Agreement.

¹¹⁷ See *id.* at 62–63.

¹¹⁸ EPC art. 53(c), *supra* note 93.

¹¹⁹ See Decision G 0002/08, 2010 O.J. Eur. Pat. Off. 1; Decision T 0024/91-3.2.02, 1994 O.J. Eur. Pat. Off. 1; **Sterckx & Cockbain**, *supra* note 95, at 157 (“[T]he exclusion of methods of medical treatment has been on societal and ethical

patient without being prevented by exclusive patent rights.”¹²⁰ Likewise courts in Europe have confirmed this focus, holding that “patent law should not interfere with the saving of human life or the alleviation of human suffering”.¹²¹

C. Methods of Treatment Under TRIPS and Other International Trade Agreements

As discussed above, the EPC establishes certain requirements regarding patent eligibility among its signatory states. Among these is the Article 53(c) exclusion of patentability for medical treatments.¹²² This approach differs from that taken by the TRIPS Agreement. Negotiations for the Uruguay round of the General Agreement on Tariffs and Trade (GATT) began in September 1986.¹²³ The treatment of intellectual property rights was always an important part of these negotiations, and in 1988 a basic framework for the treatment of intellectual property was agreed among the United States, the EU and Japan.¹²⁴ The TRIPS Agreement, which was signed in 1994 and went into effect in 1995, requires that signatory states provide minimum requirements for patentability, such as a 20-year term, non-discrimination among subject areas, national treatment for foreign applications, and the like.¹²⁵ In addition, the TRIPS Agreement permits, but does not require, the exclusion of certain categories of inventions from patent protection.¹²⁶ In particular, TRIPS Article 27(3) provides that signatories may, if they so choose, exclude from patentability “diagnostic, therapeutic and surgical methods for the treatment of humans or animals.”¹²⁷

The TRIPS approach to excluding patentability of medical treatments has been followed in numerous other multilateral and bilateral treaties, a representative list of which is included in Appendix A.¹²⁸ Several trade agreements provide this flexibility simply by referencing Article

grounds rather than on the basis that such methods could not be ‘inventions’”); Stefan Bechtold, *Physicians as User Innovators in Intellectual Property at the Edge* x, x (Rochelle Dreyfuss & Jane Ginsburg eds., 2014) (“It is now widely accepted that the exception of Article 53(c) EPC is primarily driven by ethical, moral, and public health concerns”).

¹²⁰ Bechtold, *supra* note 119, at x (Rochelle Dreyfuss & Jane Ginsburg eds., 2014) (citing European Patent Office, Tech. Bd. App., University of Manitoba/Lung ventilator device (T 0592/98), at ¶ 2 (2001), <http://www.epo.org/law-practice/case-law-appeals/advanced-search.html>; Enl. Bd. App., Cygnus/Diagnostic methods (G 1/04), [2006] E.P.O.R. 15, 161, 171; Enl. Bd. App., Medi-Physics/Treatment by surgery (G 1/07), [2010] E.P.O.R. 25, 225, 227; Tech. Bd. App., Wellcome/Pigs 1 (T 116/85), [1988] E.P.O.R. 1, 5).

¹²¹ *Id.* at x (Rochelle Dreyfuss & Jane Ginsburg eds., 2014) (citing, inter alia, Wellcome Foundation Ltd. v. Plantex, [1979] RPC 514, 540 (Eng.)).

¹²² EPC art. 53(c), *supra* note 93.

¹²³ Michael D. Wilkinson, *Lobbying for Fair Trade: Northern NGDOS, the European Community and the GATT Uruguay Round*, 17 *Third World Q.* 251, 251 (1996).

¹²⁴ *Sterckx & Cockbain*, *supra* note 95, at 50.

¹²⁵ TRIPS Agreement art. 33, *supra* note 104.

¹²⁶ Allowing, but not requiring, certain features to be incorporated into national law by signatory states is known as a treaty “flexibility.” See, e.g., TRIPS Agreement art. 27(2)-(3), *supra* note 104 (offering several such flexibilities to its signatories); Laurence R. Helfer, *Flexibility in International Agreements, in Interdisciplinary Perspectives on International Law and International Relations* 175, 175 (Jeffrey L. Dunoff & Mark A. Pollack eds., 2013) (“These [treaty flexibility] provisions function as insurance policies. They provide a hedge against uncertainty that allows a state to revise, readjust, or even renounce its commitments if the anticipated benefits of treaty-based cooperation turn out to be overblown.”).

¹²⁷ TRIPS Agreement art. 27(3), *supra* note 104.

¹²⁸ See discussion *infra* Appendix A.

27(3) of the TRIPS Agreement,¹²⁹ whereas others, such as the Trans-Pacific Partnership (TPP) Agreement, enumerate this exception expressly.¹³⁰

As noted above, the adoption of the medical treatment exclusion under TRIPS Article 27(3) influenced the negotiation of the EPC and its 2000 amendments.¹³¹ It also had a notable impact on the national laws of many other countries outside of Europe. A recent review of national laws reveals that more than sixty countries including China, Japan, and India have implemented some form of statutory patentability exclusion for medical treatments.¹³²

D. Methods of Treatment in the United States: Statutory Immunity and Patentable Subject Matter

The handling of medical treatment patents in the United States is somewhat unique and does not follow the TRIPS model outlined above.¹³³ As noted in Part II.A, the U.S. Patent and Trademark Office began to allow patents on medical treatment methods in 1954.¹³⁴ Yet few physicians availed themselves of this right or enforced their patents for several decades. This situation changed in the early 1990s, when ophthalmological surgeon Dr. Samuel Pallin applied for and received a patent covering a method of sutureless cataract surgery.¹³⁵ Shortly thereafter, as Professor Katherine Strandburg describes, Pallin began to assert the patent and seek royalties from other eye surgeons including Dr. Jack Singer.¹³⁶ Singer refused to acquiesce to Pallin's royalty demands and instead marshalled the medical community to oppose not only Singer's patent, but

¹²⁹ See, e.g., Trade Promotion Agreement, Colom.-U.S., art. 16.9, Nov. 22, 2006, <https://ustr.gov/trade-agreements/free-trade-agreements/colombia-fta/final-text> (entered into force May 15, 2012); Agreement, Peru-U.S., art. 16.9, Apr. 12, 2006, <https://ustr.gov/sites/default/files/uploads/Countries%20Regions/africa/agreements/pdfs/FTAs/peru/16%20IPR%20Legal.June%2007.pdf> ("Nothing in this Chapter shall be construed to prevent a Party from excluding inventions from patentability as set out in Articles 27.2 and 27.3 of the TRIPS Agreement.").

¹³⁰ Trans-Pacific Partnership Agreement, art. 18.37, para. 3 ("A Party may also exclude from patentability: (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals."). See Comprehensive and Progressive Agreement for Trans-Pacific Partnership art. 18.7, Feb. 4, 2016, <https://www.mfat.govt.nz/assets/Trans-Pacific-Partnership/Text/18.-Intellectual-Property-Chapter.pdf> (incorporating by reference all but 22 of the original TPP provisions, signed by the TPP countries except the United States, incorporated by reference paragraph 3 of TPP article 18.37).

¹³¹ EPC art. 53(c), *supra* note 93.

¹³² Luis Abinader, Review of National Laws Implementing Statutory Patentability Exclusions for Medical Treatments (Oct. 2018) (unpublished study) (on file with author). See list *infra* App. B (providing a complete list of these countries).

¹³³ In fact, some U.S. industry organizations have objected to the implementation of TRIPS flexibilities in this area by other countries. See, e.g., **Pharmaceutical Research and Manufacturers of America (PhRMA) Special 301 Submission 2018** 87 (2018), <https://www.phrma.org/policy-paper/phrma-special-301-submission-2018> [hereinafter **PhRMA**] (arguing that India should be included on a U.S. Department of State list of countries abusing intellectual property laws because "Section 3(i) of the Indian Patents Act excludes method of treatment claims preventing U.S. biotechnology companies with needed treatment methods from entering the Indian market and providing life-saving products").

¹³⁴ See discussion *supra* Part II.A.

¹³⁵ U.S. Patent No. 5,080,111 (filed June 28, 1990); see Strandburg, *Derogatory to Professional Character?*, *supra* note 81, at 328–29 (discussing Pallin's patent and motivations for seeking it).

¹³⁶ Pallin v. Singer, No. 2:93-CV-202, 1996 WL 274407 (D. Vt. Mar. 28, 1996) (finding that Pallin's patent was invalid and not infringed); see Strandburg, *Derogatory to Professional Character?*, *supra* note 81, at 63, 77 (discussing Pallin's case against Singer).

all patents covering medical and surgical techniques.¹³⁷ The debate soon reached a national scale and the American Medical Association issued a report in 1995 concluding that it is unethical for physicians to “seek, secure or enforce patents on medical procedures.”¹³⁸ Despite significant counter-lobbying by the biotechnology industry,¹³⁹ in 1996 Congress added Section 287(c) to the Patent Act to deal with medical treatment patents.¹⁴⁰

Unlike national statutory schemes that take advantage of the exclusionary flexibilities under TRIPS, Section 287(c) does not prohibit the patenting of medical treatments outright.¹⁴¹ Instead, it creates a limited immunity from patent infringement for medical practitioners and related healthcare entities who practice a patented “medical activity.”¹⁴² There are numerous exclusions from this immunity, including the use of a patented machine or composition of matter, the practice of a patented use of a machine or composition of matter, the practice of a process in violation of a “biotechnology patent,”¹⁴³ and the activity of any person engaged in commercial development of a machine or composition of matter.¹⁴⁴ Thus, while the U.S. approach shields physicians, hospitals, and clinics from liability for performing patented surgical, medical, and diagnostic procedures, it does not inhibit the enforcement of patents covering medical devices or drugs or against commercial interests.¹⁴⁵

Despite the immunity granted under Section 287(c), physicians, biopharmaceutical companies, and medical device manufacturers in the United States continued to obtain patents covering medical treatments in significant numbers.¹⁴⁶ But in 2012, the Supreme Court cast doubt on the patentability of certain medical procedures, particularly diagnostic methods, under Section 101 of the Patent Act. In *Mayo Collaborative Services v. Prometheus*,¹⁴⁷ the Court evaluated a patent that claimed a “method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder.”¹⁴⁸ In creating its now well-known two-part test for patent eligibility, the Court asked first whether the patent claim in question recited a law of nature and, if so, whether the claim added enough to qualify as an application of that natural law.¹⁴⁹ With respect to Prometheus’s claims, the Court held that they merely involved well-understood, routine,

¹³⁷ See Strandburg, *Derogatory to Professional Character?*, *supra* note 81, at 63, 77 (discussing medical community opposition to medical treatment patents).

¹³⁸ *Proceeding of the House of Delegates*, 144 *Am. Med. Ass’n* 1, 206 (1995), <http://www.ama-assn.org/ama/pub/about-ama/our-history/ama-historicalarchives/the-digital-collection-historical-ama-documents.page>.

¹³⁹ See Strandburg, *Derogatory to Professional Character?*, *supra* note 81, at 63, 77; see also Bradley J. Meier, *New Patent Infringement Liability Exception for Medical Procedures*, 23 *J. Legis.* 265, 265 (2015).

¹⁴⁰ Pub. L. No. 104-208, § 616, 110 Stat. 3009 (1996) (codified as amended at 35 U.S.C. § 287(c)).

¹⁴¹ TRIPS Agreement art. 27(2)-(3), *supra* note 104.

¹⁴² A “medical activity” is defined as “the performance of a medical or surgical procedure on a body.” 35 U.S.C.S. § 287(c)(2)(A) (LEXIS through Pub. L. No. 115-391).

¹⁴³ *Id.*

¹⁴⁴ 35 U.S.C.S. § 287(c)(3) (LEXIS through Pub. L. No. 115-391).

¹⁴⁵ At least one commentator has argued that the U.S. immunity under Section 287(c) violates the TRIPS Agreement. See Emily C. Melvin, Note, *An Unacceptable Exception: The Ramifications of Physician Immunity from Medical Procedure Patent Infringement Liability*, 91 *Min. L. Rev.* 1088, 1089–90 (2007).

¹⁴⁶ See, e.g., Aaron K. Chatterji et al., *Physician-Industry Cooperation in the Medical Device Industry*, 27 *Health Aff.* 1532, 1535, 1537–38 (2008) (estimating that approximately 20% of medical device patents have at least one physician inventor).

¹⁴⁷ *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 90 (2012).

¹⁴⁸ *Id.* at 74.

¹⁴⁹ *Id.*

conventional activity previously engaged in by researchers in the field, and thus failed to meet the threshold for patentability.¹⁵⁰

Much has been made of the uncertainty surrounding Section 101 patent eligibility that resulted from the Supreme Court's holding in Mayo and its 2014 decision in Alice v. CLS Bank.¹⁵¹ A number of

U.S. courts have invalidated medical treatment patents under Section 101 after applying the two-step test established in Mayo. For example, in Mallinckrodt Hospital Prods. IP Ltd. v. Praxair Distrib., Inc.,¹⁵² the court considered the following patent claim:

1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

- (a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;
- (b) determining that a first patient of the plurality does not have left ventricular dysfunction;
- (c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;
- (d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and
- (e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.¹⁵³

The court found this claim to be patent ineligible under Section 101 on the basis that the “core” of the alleged invention, treatment of hypoxic respiratory failure with inhaled nitric oxide, was a patent ineligible law of nature.¹⁵⁴ And as to whether the claim added anything of significance to this natural law, the court concluded “Plaintiffs cannot seriously contend that it is a new practice

¹⁵⁰ Id. at 77–80.

¹⁵¹ See Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 212 (2014) (holding that a computer program for facilitating complex international financial transactions is an abstract idea that cannot be patented). For critiques of these decisions, see, e.g., Kevin Madigan & Adam Mossoff, Turning Gold into Lead: How Patent Eligibility Doctrine is Undermining U.S. Leadership in Innovation, 24 Geo. Mason L. Rev. 939, 950–52 (2017); Dan L. Burk, Dolly and Alice, 3 J. L. & Biosciences 606, 609–11 (2015).

¹⁵² Mallinckrodt Hosp. Prods. IP Ltd. v. Praxair Distribution, Inc., Civil Action No. 15-170-GMS, 2017 U.S. Dist. LEXIS 142644, at *19 (D. Del. Sept. 5, 2017).

¹⁵³ Id.

¹⁵⁴ Id. at *60.

to exclude certain patients from treatment with a drug when those patients are at an increased risk of experiencing negative side effects from the drug.”¹⁵⁵ Thus, the claim was not patent eligible.¹⁵⁶

In contrast, the Federal Circuit in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals*¹⁵⁷ held that a method of treating a patient with schizophrenia by determining the patient’s capacity to metabolize a particular enzyme and then administering a particular dosage of a drug containing the enzyme based on that finding.¹⁵⁸ Despite the similarity of the method claims in *Vanda* to those in *Mayo* itself, the Federal Circuit held that the claims were not directed to a natural law or phenomenon.¹⁵⁹ According to at least one commentator, “*Vanda* precipitated a 180-degree turn in how district courts deal with patent-eligibility challenges to method of treatment claims. Whereas pre-*Vanda* the district courts typically found these claims to be directed to a law of nature under step one [of *Mayo*], they now uniformly find them patent-eligible under step one and do not proceed to step two.”¹⁶⁰

Likewise, the USPTO has issued guidance stating that, consistent with *Vanda*, “method of treatment claims that practically apply natural relationships should be considered patent eligible under Step [1] [of *Mayo*].”¹⁶¹ Most recently, the Federal Circuit in *Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*¹⁶² upheld the eligibility of another personalized method of treatment claim involving the dosing of a particular drug based on a patient’s metabolic characteristics.

Given these developments, the current trend in the U.S. appears to be to recognize the patentability of medical treatment claims, subject only to the limited healthcare practitioner immunity under Section 287(c).

E. Other Jurisdictions and Limits on Patentability of Medical Treatment

In addition to the jurisdictions discussed above, some jurisdictions that have not expressly adopted statutory limitations on the patenting of medical treatments have limited such patents through judicial doctrine. In Canada, for example, the Canadian Patent Act does not expressly exclude medical treatments from patentability.¹⁶³ However, the Canadian Supreme Court has rejected patents covering medical treatments when the claimed method “does not lay in the field of the manual or productive arts nor, when applied to the human body, does it produce a result in

¹⁵⁵ *Id.* at *54.

¹⁵⁶ *Id.* at *60.

¹⁵⁷ *Vanda Pharms. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018).

¹⁵⁸ *Id.*

¹⁵⁹ *Id.* Judge Prost dissented from the decision, pointing out the clear analogy to the claims in *Mayo*. *Id.* at x.

¹⁶⁰ Thomas Hedemann & David Ludwig, *Method-Of-Treatment Patent Eligibility: Step 1 And Done?* *Law360*, Feb. 5, 2019.

¹⁶¹ Robert W. Bahr, *Recent Subject Matter Eligibility Decision: Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals* (2018).

¹⁶² *Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.* (Fed. Cir. 2019).

¹⁶³ *See* Canada Patent Act, R.S.C. 1985, c P-4 (authorizing the use of a patented invention only if “the Minister of Health has notified the Commissioner that the version of the pharmaceutical product that is named in the application meets the requirements of the *Food and Drugs Act* and its regulations, including the requirements under those regulations relating to the marking, embossing, labeling and packaging that identify that version of the product as having been manufactured . . . in a manner that distinguishes it from the version of the pharmaceutical product sold in Canada by, or with the consent of, the patentee or patentees”).

relation to trade, commerce or industry, or a result that is essentially economic.”¹⁶⁴ In effect, this approach resembles the pre-EPC approach taken by courts in the UK, which found that medical treatments were not patentable due to their lack of industrial application.¹⁶⁵ The Canadian Patent Office has adopted this judicial reasoning in its examination procedures and now rejects patent claims seeking to cover methods that provide a practical therapeutic effect, such as curing, preventing, or ameliorating an ailment or pathological condition, or treating a physical abnormality or deformity, such as by physiotherapy or surgery.¹⁶⁶

Likewise, though New Zealand did not statutorily limit the patentability of medical treatments until recently,¹⁶⁷ the New Zealand courts consistently held that methods of treatment of human disease do not meet the requirement that patentable methods describe a manner of manufacture.¹⁶⁸

The one developed jurisdiction that appears most willing to grant and enforce medical treatment patents is Australia. The Australian Federal Court first confirmed the patentability of medical treatment methods in 1994 in Anaesthetic Supplies v. Rescare and confirmed this result in 2000 in Bristol Myers Squibb v. F H Faulding.¹⁶⁹ The Court’s decision in Bristol Meyers Squibb, a case involving a method of administering the anti-cancer drug Taxol, is particularly telling. In that case, the lower court, relying on a dissenting opinion in Rescare, held that issuing a patent on the claimed treatment method was “generally inconvenient” under the public policy proviso of the Australian Statute of Monopolies, and that the patent was thus invalid.¹⁷⁰ The Federal Court unanimously reversed the lower court’s decision, finding no reason to deviate from its prior reasoning in Rescare. Most recently, an Australian High Court again confirmed the patentability of methods of treatment involving the administration of therapeutic drugs in Apotex v. Sanofi-Aventis Australia.¹⁷¹ Interestingly, each of these decisions involved method claims describing the administration of a therapeutic agent or drug. The Australian courts have yet to confirm the patentability of purely medical or surgical procedures.¹⁷²

¹⁶⁴ Apotex Inc. v. Wellcome Found. Ltd. [2002] S.C.R. 153 (Can.) (“The policy rationale . . . was that the unpatentable claim was essentially non-economic and unrelated to trade, industry, or commerce. It was related rather to the area of professional skills.”); Tennessee Eastman v. Commissioner of Patents [1974] S.C.R. 111 (Can.); Commissioner’s Decision, No. 197, at 2 (1974) (Can.), <http://brevets-patents.ic.gc.ca/opic-cipo/comdec/eng/decision/194/image.html?page=1&scale=0.25&rotation=0> (“Having come to the conclusion that methods of medical treatment are not contemplated in the definition of ‘invention’ as a kind of ‘process’”).

¹⁶⁵ David Letham & Richard Scott, The Doctrine of Equivalents Reaches the UK 1–2 **Hoffmann Eitle**, <https://www.hoffmann-eitle.com/wp-content/uploads/The-Doctrine-Of-Equivalents-Reaches-the-UK.2-1.pdf>.

¹⁶⁶ **Can. Intell. Prop. Off., Patent Office Manual of Patent Office Practice** (2018), [https://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/vwapj/rpbb-mopop-eng.pdf/\\$file/rpbb-mopop-eng.pdf](https://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/vwapj/rpbb-mopop-eng.pdf/$file/rpbb-mopop-eng.pdf) (explaining that section 17.03.01 notes, however, that “removal of the medical aspect of a claim may render [the claim] acceptable”).

¹⁶⁷ Patents Act 2013, s 2 (N.Z.) (“An invention of a method of treatment of human beings by surgery or therapy is not a patentable invention.”).

¹⁶⁸ Swift & Co. [1960] NZIPOPAT 1 (1960) (N.Z.); Wellcome Found. Ltd. v. Comm’r of Patents [1983] NZCA 385 (N.Z.); Susy Frankel, Intellectual Property in New Zealand and the TPPA 173–74 (Victoria Univ. of Wellington, Legal Research Paper No. 37, 2012) (“The Patent Bill before Parliament at the time of writing includes some exceptions to patentability because these things should not be the exclusive property of anyone.”).

¹⁶⁹ Bristol-Myers Squibb Co. v. F H Faulding & Co. Ltd. [2000] FCA 316 (22 March 2000) ¶¶ 132–39 (Austl.).

¹⁷⁰ Id. ¶¶ 5–7.

¹⁷¹ Apotex Pty. Ltd. v. Sanofi-Aventis Australia Pty. Ltd. [2013] HCA 50 (4 December 2013) (Austl.).

¹⁷² It is important to note that medical treatments are not always patentable under Australian law. Each patent claim must be addressed on a case-by-case basis. See, e.g., id.

F. Summary: Methods of Medical Treatment Patentability Exclusions

As shown in this Part II, numerous jurisdictions have limited the ability of applicants to obtain patents on methods of medical treatment. The EPC expressly removes medical treatments from patentability and has been followed by all EPC member states.¹⁷³ The TRIPS Agreement and numerous other bilateral and multilateral trade agreements allow signatory states to exclude medical treatments from their national patent laws, and at least sixty states have taken advantage of this flexibility to do so.¹⁷⁴ The United States, in contrast, has adopted a unique statutory immunity from infringement for medical practitioners and healthcare organizations, but it otherwise likely to uphold patents on medical treatments. Other countries, though they have not enacted specific legislation limiting medical treatment patents, have taken a range of judicial positions that have failed to uphold such patents on grounds of lack of industrial application. As a result, the patentability of medical treatments is effectively prohibited or limited throughout much of the developed world.

III. ARE CAR-T AND OTHER GENE THERAPIES PATENTABLE?

Given the extensive limitations on patenting medical treatments around the world, we ask whether CAR-T and other gene therapies discussed in Part I should be considered medical treatments subject to such limitations. In analyzing this question, it is important first to develop a more detailed understanding of the definition “medical treatment.” While we are unaware of any court or agency decision applying this definition specifically to CAR-T therapies, several useful discussions exist in the case law and literature.

A. Methods of Medical Treatment under the EPC Exclusion

As described in Part II.B, Article 53(c) of the EPC excludes medical treatments from patent protection on grounds of ordre public and morality.¹⁷⁵ Over the years, the courts and the European Patent Office (EPO), including the EPO’s Boards of Appeal,¹⁷⁶ have interpreted the Article 53(c) exclusion (including its precursor under Article 52[4]) and its subcomponents. In this Part III.A, we discuss the decisions of these bodies inasmuch as they are relevant to the patentability of gene and cell therapies, which we take up specifically in Part III.B, below.¹⁷⁷

¹⁷³ EPC art. 53(c), *supra* note 93.

¹⁷⁴ World Intellectual Prop. Org. [WIPO], Exclusions from Patentable Subject Matter and Exceptions and Limitations to the Rights, at 58, WIPO Doc. SCP/15/3 (Jan. 1, 2010); Mitnovetski & Nicol, *supra* note 79, at 470.

¹⁷⁵ Mitnovetski & Nicol, *supra* note 79, at 472.

¹⁷⁶ Decisions of the EPO are reviewed by one of twenty-eight Technical Boards of Appeal, with appellate recourse to an Enlarged Board of Appeal. See About the Boards of Appeal, Eur. Pat. Off., <https://www.epo.org/law-practice/case-law-appeals/about-the-boards-of-appeal.html> (last visited Feb. 12, 2019). Decisions of the EPO are not strictly binding on national courts, which have the ultimate authority to interpret their national patent statutes and to assess the patentability of inventions under those statutes. However, decisions of the EPO, and its Board of Appeal in particular, are viewed as highly informative to national courts interpreting their national laws implementing the EPC.

¹⁷⁷ For a comprehensive discussion of the EPC’s medical treatment exclusion, see Sterckx & Cockbain, *supra* note 95, at 135–71.

1. Performance by a Medical Practitioner

The EPO Boards of Appeal have defined the term “medical treatment” as “any non-insignificant intentional physical or psychic intervention performed directly or indirectly by one human being—who need not necessarily be a medical practitioner—on another . . . using means or methods of medical science.”¹⁷⁸ The Boards of Appeal have explained that a medical treatment need not be carried out by a physician in order to fall within the exclusion.¹⁷⁹ However, the Boards have also suggested that there is a strong presumption that a method is excluded under the EPC when that method has to be performed by a physician or under his or her supervision.¹⁸⁰

2. Practiced on the Human Body

To fall within the exclusion provided under EPC Article 53(c), the method of treatment must be “practised on the human or animal body.”¹⁸¹ However, Article 53(c) “does not require a specific type and intensity of interaction with the human or animal body.”¹⁸² According to the EPO Boards of Appeal, a method claim falls under the prohibition if it includes at least one feature defining a physical activity or action that constitutes a method step for treatment of the human or animal body by surgery or therapy.¹⁸³ Indeed, according to the EPO Boards of Appeal, “[T]he surgical or therapeutic nature of a method claim can perfectly be established by a single method step”¹⁸⁴ This “single step” threshold is also recognized in the November 2018 edition of the EPO Guidelines for Examination.¹⁸⁵

¹⁷⁸ Case T 0182/90 (Blood flow), ECLI:EP:BA:1993:T018290.19930730, ¶ 2.2 (July 30, 1993), <https://www.epo.org/law-practice/case-law-appeals/recent/t900182ex1.html>.

¹⁷⁹ *Id.*; see *Sterckx & Cockbain*, *supra* note 95, at 156.

¹⁸⁰ Case T 0024/91 (Cornea), ECLI:EP:BA:1994:T002491.19940505, ¶ 2.4 (May 5, 1994), <https://www.epo.org/law-practice/case-law-appeals/recent/t910024ex1.html> (“[W]here, in view of the health risks connected with such a treatment, a claimed method for treatment has to be performed by a physician or under his supervision, it will normally fall within the exclusion of the first sentence of Article 52(4) EPC.”); Case T 0329/94 (Blood extraction method), ECLI:EP:BA:1997:T032994.19970611, ¶ 5 (June 11, 1997), <https://www.epo.org/law-practice/case-law-appeals/recent/t940329ex1.html> (“This sole criterion is not sufficient to decide whether the method step is objectionable under Art. 52(4) EPC, though the medical competence of the practitioner may be, at first sight, a useful indication. Much more important are the purpose and inevitable effect of the feature under consideration.”).

¹⁸¹ *Guidelines for Examination in the European Patent Office*, *Eur. Pat. Off.*, at Part G, ch. 2, § 4.2.1 (2018), [http://documents.epo.org/projects/babylon/eponet.nsf/0/2A358516CE34385CC125833700498332/\\$File/guidelines_for_examination_2018_hyperlinked_en.pdf](http://documents.epo.org/projects/babylon/eponet.nsf/0/2A358516CE34385CC125833700498332/$File/guidelines_for_examination_2018_hyperlinked_en.pdf).

¹⁸² See, e.g., Case G 0001/04 (Diagnostic methods), ECLI:EP:BA:2005:G000104.20051216, ¶ 6.4.2 (Dec. 16, 2005), <https://www.epo.org/law-practice/case-law-appeals/recent/g040001ex1.html> (“It follows that each and every one of these method steps satisfies the criterion ‘practised on the human or animal body’ if its performance implies any interaction with the human or animal body, necessitating the presence of the latter.”).

¹⁸³ *Id.* This principle is known as the “contamination” approach, as any single medical treatment step will “contaminate” the entire claim and render it unpatentable. *Sterckx & Cockbain*, *supra* note 95, at 159 (“To have done otherwise would have made a mockery of the exclusion—if cutting off a man’s leg is surgery, then does giving him a cup of tea afterwards mean he has not undergone surgery?”).

¹⁸⁴ See Case G 0001/04 (Diagnostic methods), ECLI:EP:BA:2005:G000104.20051216, at ¶ 6.2.1; see also G 2/08, O.J. EPO 2010, 456 at 476, ¶ 5.6. (“[A]ny method claim containing even a single step pertaining by nature to a treatment by therapy is not allowable. This is established case law.”).

¹⁸⁵ *Guidelines for Examination in the European Patent Office*, *supra* note 168, at Part G, ch. 2, § 4.2.1.

However, claims that disclose methods carried out fully *in vitro*, without requiring that at least one of the steps be practiced on the human or animal body, do not fall within the Article 53(c) exception.¹⁸⁶ Thus, as explained by Sterckx and Cockbain,

It has long been clear that *ex vivo* diagnostic methods (e.g. diagnostic tests performed on blood samples) as well as the substances and equipment used by physicians and veterinary surgeons in the course of diagnosis, therapy and surgery, were not and are not excluded from patentability.¹⁸⁷

3. *Surgery or Therapy*

In order to be excluded from patentability, Article 53(c) requires that the method of treatment be implemented by means of “surgery or therapy.”¹⁸⁸ Several forms of medical intervention have been considered by the EPO Boards of Appeal to fall within the meaning of the term “therapy” for purposes of applying this exception. The Board has applied this exception to patent applications claiming curative therapies, or methods for the healing of diseases,¹⁸⁹ but also for methods aimed at relieving pain, or symptomatic therapy,¹⁹⁰ and methods designed to prevent diseases from occurring, also known as prophylactic therapy.¹⁹¹

4. *Removal from the Body*

The EPO Guidelines for Examination explain that the treatment of body tissue or fluids “after they have been removed from the human or animal body, or diagnostic methods applied thereon, are not excluded from patentability as long as these tissues or fluids are not returned to the same body.”¹⁹² By the same reasoning, the treatment of body tissue or fluids that are returned to the same body are subject to the exclusion contained in Article 53(c).¹⁹³ An example given by the EPO Guidelines involves fluids removed from the body: the treatment of blood for storage in a blood bank or diagnostic testing of blood samples are generally not excluded from patentability, while the treatment of blood by dialysis with the blood being returned to the same body, are generally excluded from patentability under Article 53(c).¹⁹⁴ Accordingly, it is the return of tissues or fluids to the same body from which they were originally taken that bring a process within the patentability exclusion of Article 53(c).¹⁹⁵

¹⁸⁶ Case G 0001/04 (Diagnostic methods), ECLI:EP:BA:2005:G0001045.20051216, ¶ 6.4.3. (“[T]his criterion is neither complied with in respect of method steps carried out *in vitro* in a laboratory.”).

¹⁸⁷ **Sterckx & Cockbain**, *supra* note 95, at 158.

¹⁸⁸ *See id.* at 138–52 (discussing cases defining therapy and surgery).

¹⁸⁹ Case T 0019/86 (Pigs II), ECLI:EP:BA:1987:T001986.19871015, ¶ 8 (Oct. 15, 1987), <https://www.epo.org/law-practice/case-law-appeals/recent/t860019ep1.html>.

¹⁹⁰ Case T 0081/84 (Dysmenorrhea), ECLI:EP:BA:1987:T008184.19870515, ¶ 4 (May 15, 1987), <https://www.epo.org/law-practice/case-law-appeals/recent/t840081ex1.html>.

¹⁹¹ *See* Case T 0019/86 (Pigs II), ECLI:EP:BA:1987:T001986.19871015, ¶ 7.

¹⁹² Guidelines for Examination in the European Patent Office, *supra* note 168, at Part G, ch. 2, § 4.2.1.

¹⁹³ *Id.*

¹⁹⁴ *Id.* (“Thus the treatment of blood for storage in a blood bank or diagnostic testing of blood samples is not excluded, whereas a treatment of blood by dialysis with the blood being returned to the same body would be excluded.”).

¹⁹⁵ *Id.*

5. *Product versus Process Claims*

Much of the controversy surrounding medical treatment patents has arisen with respect to methods of administering particular drugs (i.e., patient selection, dosing regimen, etc.). While Article 53(c) of the EPC prohibits the patenting of medical treatments, it expressly does not apply to “products, in particular substances or compositions, for use in any of these methods.”¹⁹⁶ As explained by the EPO Enlarged Board of Appeals,

The provisions of Article 53(c) EPC are clear and unambiguous, drawing a borderline between unallowable method claims directed to a therapeutic treatment on the one hand and allowable claims to products for use in such methods on the other hand . . . [Thus,] in respect of claims directed to therapy, method claims are absolutely forbidden in order to leave the physician free to act unfettered, whereas product claims are allowable provided their subject-matter be new and inventive.¹⁹⁷

Despite the seeming clarity of this distinction, the division between treatment methods and products became blurred in the case of patent claims covering methods for the administration of particular drugs, especially drugs that were themselves unpatented.¹⁹⁸ This issue was addressed, to a degree, in the 2000 amendments to the EPC, which added Article 54(5) providing that methods of treatment involving a new use of a known substance were amenable to patent protection, notwithstanding the limitations of Article 53(c).¹⁹⁹ The EPO Enlarged Board of Appeal has since clarified that such new uses can encompass any “specified new and inventive therapeutic application” (e.g., new dosage regimes) and need not be drawn to entirely new diseases than the substance was previously known to address.²⁰⁰

B. Applying the EPC Patentability Exclusion to Gene Therapies

Article 53(c) of the EPC has important implications for the patentability of gene and cell therapies at the EPO. In this Part, we analyze the features of CAR-T patent claims in view of the patentability exclusion under EPC Article 53(c) and conclude that such claims are largely encompassed by this exclusion. It seems that we are not alone in this assessment: even

¹⁹⁶ EPC art. 53(c), *supra* note 93.

¹⁹⁷ See G 2/08, OJ EPO 2010, at 477, ¶ 5.7.

¹⁹⁸ Carlos Correa, **Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective** – A Working Paper 16 (Jan. 27, 2007), <http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf>.

¹⁹⁹ EPC art. 54(5), *supra* note 93 (“Paragraphs 2 and 3 [relating to novelty] shall also not exclude the patentability of any substance or composition [comprised in the state of the art] for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art.”). See *Sterckx & Cockbain*, *supra* note 95, at 159.

²⁰⁰ See G 2/08, OJ EPO 2010, at 485, ¶ 5.10.5. Prior to the 2000 EPC amendments and the EPO Enlarged Board of Appeal’s decision in G 0002/08, many applicants drafted claims for new uses of known substances in terms of a manufacturing process for the substance (so-called “Swiss-type claims”). The Board eliminated the permissibility of such Swiss-type claims in G 0002/08 given the clarified language of EPC Article 54(5). G 2/08, OJ EPO 2010, at 492, ¶ 7.1.3.

representatives of the biopharmaceutical industry appear to recognize that gene and cell therapies such as CAR-T are better characterized as medical procedures than drugs, which then leads to the question of what type of intellectual property protection, if any, applies. During a panel of the Fifth Global Congress on Intellectual Property and the Public Interest, Joseph Damond, Senior Vice President of the Biotechnology Industry Organization (BIO), stated:

What I'm concerned about, then, is not just where we stand now, but where the future of the industry is going. Because, if you look at those pipelines, what's being done right now are things like gene therapy and cell therapy, where you take your blood and give it to a company and they modify your DNA to correct for mutations and they give it back to you, which looks more like a service, actually, than a drug. And what's the IP on that?²⁰¹

The remainder of this Part explores this question.

1. In vivo versus in vitro procedures

Gene therapies involve introducing, removing or changing the content of a person's genetic code.²⁰² Cell therapy involves administering living cells to a patient.²⁰³ Therefore, patent claims covering gene and cell therapies are often drafted using method claims where at least one of the steps is performed *in vivo*.²⁰⁴ In such cases, these method claims, including methods of performing CAR-T therapy, can be considered methods "practiced on the human or animal body," therefore falling under the exclusion provided in EPC Article 53(c).²⁰⁵

Although gene and cell therapies, including CAR-T, may also involve *ex vivo* steps in which genes and cells are harvested or modified outside the human body, EPC Article 53(c) does not require all of the method steps to be practiced on the patient in order to be considered a method of treatment.²⁰⁶ As the EPO Boards of Appeal has explained, "the surgical or therapeutic nature of a method claim can perfectly be established by a single method step"²⁰⁷

It is precisely one of the method steps, the reintroduction of the cells to the same patient from which they were previously extracted, that better illustrate why CAR-T method patent applications likely fall under EPC Article 53(c). As noted in Part II.A.4 above, the EPO Guidelines distinguish between methods that only involve extracting body tissues or fluids from methods that

²⁰¹ O'Neill Institute, *Global Congress on Intellectual Property & The Public Interest*, **YouTube** (Oct. 10, 2018), <https://www.youtube.com/watch?v=OkuSLYIxbg&feature=youtu.be&t=2175>.

²⁰² *Gene and Cell Therapy Defined*, **Am. Soc'y Gene & Cell Therapy**, <https://www.asgct.org/education-legacy/gene-and-cell-therapy-defined> (last visited Feb. 13, 2019).

²⁰³ *Id.*

²⁰⁴ Gregory Ramina, *Regulation and Oversight of Gene Therapy in the US*, **Regulatory Focus** 2 (Feb. 2017), https://advanced.jhu.edu/wp-content/uploads/2017/03/gregoryRamina_regulationAndOversightOfGeneTherapyInTheUS.pdf.

²⁰⁵ EPC art. 53(c), *supra* note 93; Ramina, *supra* note 191, at 2.

²⁰⁶ EPC art. 53(c), *supra* note 93; Ramina, *supra* note 191, at 2.

²⁰⁷ Case G 0001/04 (Diagnostic methods), ECLI:EP:BA:2005:G000104.20051216, ¶ 6.4.3 (Dec. 16, 2005), <https://www.epo.org/law-practice/case-law-appeals/recent/g040001ex1.html>.

also involve reintroducing the extracted tissues or fluids to the same patient, such as dialysis.²⁰⁸ The last example closely resembles the apheresis and cell infusion steps that are required in CAR-T therapies.²⁰⁹

Despite the original focus of CAR-T patents on compositions of matter,²¹⁰ there are numerous examples today of EPO applications for CAR-T and other gene therapies that read in terms of methods of treatment. For example, one claim of a 2014 PCT application submitted by Dr. Carl June, a CAR-T pioneer at the University of Pennsylvania, reads as follows:

A method for inducing at least a first and second epitope-specific immune response in a cancer patient, the method comprising administering to a patient in need thereof an effective amount of a cell genetically modified to express a chimeric antigen receptor (CAR) comprising an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the first epitope-specific immune response is directed to a target epitope recognized by the CAR.²¹¹

This claim encompasses (a) a method (b) for inducing an immune response (c) by administering a cell genetically modified to express a CAR, and (d) a description of the cell.²¹² As such, this claim appears highly susceptible to interpretation as a method of medical treatment.

There is at least one EPO application disclosing a CAR in which the examiner raised Article 53(c) objections against two of the claims.²¹³ The first EPO opinion for this application rejected the claims, reasoning that:

Claims 18 and 19 refer to a method of modulating the activity of a T lymphocyte in vivo. This is considered as a method of treatment practiced on the human or animal body. Pursuant to Art. 53(c) EPC, the subject-matter of said claims is not regarded as being patentable. Consequently, said claims should be either deleted or reformulated appropriately.²¹⁴

²⁰⁸ Guidelines for Examination in EPO, *supra* note 168, at Part G, ch. 2, § 4.2.1.

²⁰⁹ What is the Process of Getting Treated with CAR T Cell Therapy?, **Be The Match: CAR T Cell Therapy**, <https://bethematch.org/patients-and-families/about-transplant/clinical-trials/car-t-cell-therapy/> (last visited Feb. 15, 2019).

²¹⁰ See *infra* note 215 and accompanying text.

²¹¹ U.S. Patent Application No. 14/409,798 claim 1 (published Aug. 18, 2016).

²¹² Id. (claiming that an effective amount of genetically modified cells needs to be administered to the patient to express a CAR).

²¹³ European Patent Specification, European Patent Office App. No. 14751227.1, Publication No. EP2 956175B1, at 3 (published Oct. 4, 2017).

²¹⁴ Examination, European Patent Office App. No. 14751227.1, ¶ 5.1 (filed on Mar. 22, 2016), <https://register.epo.org/application?number=EP14751227&lng=en&tab=doclist> (select “Search/examination” in drop down menu and then scroll down to find a document dated “25.07.2016” and titled “European search opinion”).

Following this opinion, the applicant amended its claims to eliminate the term *in vivo* and replaced it with the term *in vitro*.²¹⁵ After these changes, the application was allowed.²¹⁶ It appears that, in the opinion of the examiner, amending the claims to suggest that that specific step of the method was conducted “*in vitro*” as opposed to “*in vivo*” was sufficient to avoid the “practised on the human . . . body” threshold of Article 53(c).²¹⁷ This reasoning appears questionable. Clearly, whatever alterations are made to the patient’s T-cells outside of the body, the cells must eventually be returned to the patient’s body to be effective. As such, the CAR-T process described in the claims more closely resembles a procedure like dialysis (in which cells are treated and then returned to the body) than storage of cells for biobanking (in which cells are removed from the body and not returned).²¹⁸ Simply diverting attention to the *in vitro* aspect of the procedure does not eliminate all of its *in vivo* elements and, as noted above, only one *in vivo* step of a process is required in order to classify it as a medical treatment.²¹⁹

2. Process versus Product

Another question regarding the applicability of Article 53(c) to CAR-T and other gene therapies is whether such technologies are more likely to be classified as treatments or products. As noted in Part II.B.5 above, the patentability exclusion of EPC Article 53(c) does not apply to therapeutic compounds or substances, a compromise reached during the negotiation of the EPC to preserve the patentability of pharmaceutical products.²²⁰ But as discussed above in this Part III.B, CAR-T and other gene therapies resemble medical treatments in many ways: they are designed to treat disease by taking action on a patient’s body through the removal, treatment, and replacement

²¹⁵ Claim 18 and 19 of EPO patent application EP2956175 currently reads as follows:

“18. A genetically modified cell according to claim 10 or 11 for use in a method of treatment of a cancer in an individual, wherein the conditionally active CAR is specific for an epitope on a cancer cell in the individual, and wherein the method comprises: i) introducing the genetically modified cell into the individual; and ii) administering to the individual an effective amount of a dimerizing agent, wherein the dimerizing agent induces dimerization of the heterodimeric, conditionally active CAR, wherein said dimerization provides for activation of the genetically modified cell and killing of the cancer cell, thereby treating the cancer.”

“19. A method of modulating the activity of a T lymphocyte host cell, the method comprising contacting the host cell *in vitro* or *ex vivo* with a dimerizing agent and a second member of a specific binding pair, wherein the T lymphocyte is genetically modified to produce a heterodimeric, conditionally active CAR of any one of claims 1 to 9, and wherein, in the presence of the dimerizing agent and the second member of a specific binding pair, the heterodimeric, conditionally active CAR dimerizes and modulates at least one activity of the host cell.” European Patent Specification, European Patent Office App. No. 14751227.1, *supra* note 200, at 149.

²¹⁶ See Communication under Rule 71(3) EPC, European Patent Office App. No. 14751227.1, Ref. No. AHB/FP7144538 (May 9, 2017).

²¹⁷ *Id.*; EPC art. 53(c), *supra* note 93.

²¹⁸ European Patent Specification, European Patent Office App. No. 14751227.1, *supra* note 200, at 149 (stating that a genetically modified cell is introduced into the individual’s body as treatment for the cancer).

²¹⁹ Furthermore, even in their current form, the application still appears to claim steps that likely consist of a method of treatment, even if it now does not use the term “*in vivo*.” That is the case, for example, with the phrase “introducing the genetically modified cell into the individual” as provided in the current version of the claims. European Patent Office Application No. 14751227.1, *supra* note 200, at 149. See Sherkow et al., *supra* note 16 (“our definition [of gene therapy] is agnostic as to whether such modification takes place inside patient’s body or, as with CAR-T, outside of it”).

²²⁰ See Guidelines for Examination in the European Patent Office, *supra* note 168, at Part G, ch. 6, § 7.1.2; see also discussion *supra* Part II.B.5.

of the patient's own cells.²²¹ In this regard, such therapies resemble dialysis and other medical procedures that are generally acknowledged as excluded from patentability under Article 53(c).²²² In fact, Kite Pharma, the developer of Yescarta, explicitly describes its patents as covering "methods of treatment" in its public securities filings.²²³

However, in their regulatory filings, the developers of CAR-T therapies have gone to great lengths to refer to these therapies not as medical treatments, but as products. For example, as discussed in Part I.C, both the U.S. FDA and the EU EMA give considerable weight to the "manufacturing" practices proposed for new gene therapies.²²⁴ Novartis, in its FDA application for marketing approval of Kymriah, consistently refers to Kymriah (tisagenlecleucel) as a "product" that is "manufactured" at a facility in New Jersey,²²⁵ much as a traditional drug would be. The documentation published by the European Medicine Agency (EMA) also describes Kymriah as a "product."²²⁶

This characterization of Kymriah as a product or drug, however, is a fiction.²²⁷ The "product" in question is a batch of the patient's own T-cells that are taken from the patient, altered, and then re-introduced into the patient's body.²²⁸ This is not a manufactured product, but a process performed ex vivo on the patient's cells.²²⁹

The "labeling" of a "product" like Kymriah pushes this fiction to its limit, as the "product" in question is not sold or marketed to the public, patients, pharmacists, or physicians, but rather is extracted from a particular individual for eventual re-introduction to the donor individual alone, and to no one else.²³⁰ As such, the "packaging" in which Kymriah is approved to be "marketed" is the intravenous infusion bag used to reintroduce the modified T-cells to the patient's body.²³¹ This

²²¹ See Chimeric Antigen Receptor (CAR) T-Cell Therapy, Leukemia and Lymphoma Soc'y, <https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy> (last visited Feb. 17, 2019); see also discussion supra Part III.B.

²²² What is CAR-T Cell Therapy?, Penn. Medicine: Abramson Cancer Ctr. (Dec. 4, 2017), <https://www.pennmedicine.org/cancer/about/focus-on-cancer/2017/december/defining-cart>; Guidelines for Examination in the European Patent Office, supra note 168, at Part G, ch. 2, § 4.2.1.

²²³ **Kite Pharma, Inc., Annual Report (Form 10-K)** 16 (Feb. 28, 2017) ("Our intellectual property estate strategy is designed to provide multiple layers of protection, including: (1) patent rights with broad claims directed to core CAR constructs used in our products; (2) patent rights covering methods of treatment for therapeutic indications; (3) patent rights covering specific products; and (4) patent rights covering innovative manufacturing processes, preconditioning methods, new constructs and methods for genetically engineering T cells.") (emphasis added).

²²⁴ **Richard Kingham et al., Biological Drug Products: Development and Strategies** 85, 92 n.65, 97–98 (Wei Wang & Manmohan Singh eds., 2014).

²²⁵ **Novartis Approval Letter**, supra note 3, at 1.

²²⁶ European Medicine Agency [EMA], Annex I: Summary of Product Characteristics, at 2, https://www.ema.europa.eu/documents/product-information/kymriah-epar-product-information_en.pdf (last visited Feb. 17, 2019).

²²⁷ We recognize that the tendency for manufacturers to characterize their gene therapies as "products" is also due to the statutory authority of the FDA, which regulates products and their manufacture, but not medical procedures. But even if there is an extrinsic reason pushing manufacturers to categorize these methods as products, the classification is still, in our view, a fiction.

²²⁸ See id. at 39 (describing the process of how the doctor will remove the patient's white blood cells, process them to make Kymriah, and then return the substance to the patient's body).

²²⁹ Id. at 2. This being said, we recognize that the producers of CAR-T and other gene and cell therapies have drafted some of their patent claims to cover modified T-cells and other biological compounds as compositions of matter. While these types of claims might appear to avoid exclusion under the medical treatment provisions discussed in this article, we suggest that the examining patent offices look past artful claiming to the actual invention for which a patent is sought—in this case, a method of medical treatment.

²³⁰ See id. at 36, 39 (explaining the unique characteristics of Kymriah and how the product is formed).

²³¹ See id. at 39 (describing how Kymriah will be stored and labeled).

is hardly “marketing” of a product, given that no individual—patient, pharmacist, or physician—need make any purchasing or prescribing decision regarding the re-administration of the modified T-cells back to the patient.²³² Thus, referring to a CAR-T therapy such as Kymriah as a product that is packaged and marketed simply mischaracterizes the nature of the therapy and inaccurately conflates it with a drug product that is marketed and prescribed to members of the public. While this characterization appears to be acceptable to the FDA and EMA which encourages applicants to apply the language of “products” to new gene therapies in its Guidance documents,²³³ this peculiar regulatory approach should not alter the more accurate characterization of such gene therapies as medical treatments under the patent laws, which stand quite apart from the requirements for regulatory marketing approval.

C. CAR-T and Gene Therapies Beyond the EPC

As discussed in Part III.B above, CAR-T and other gene and cell therapies should most likely be classified as medical treatments under the EPC and thus excluded from patentability under EPC Article 53(c). By the same token, such therapies should also be excluded from patentability under other legal regimes that exclude patents on medical treatments, including (a) national implementations of EPC Article 53(c), (b) national patent laws that implement the flexibility to exclude such patents under TRIPS Article 27(3) and other bilateral and multilateral trade agreements, and (c) judicial precedents, such as those in Canada and New Zealand, that exclude patentability of medical therapies as lacking industrial application or as against ordre public and morality. In addition, in the United States CAR-T and other gene and cell therapies should trigger the immunity from infringement for physicians and healthcare organizations under Section 287(c) of the U.S. Patent Act.

Admittedly, outside of the EPC and U.S., there is little case law or agency guidance regarding the scope of the medical treatment exemption, and even less that informs its application to gene and cell therapies. However, we believe that the detailed reasoning of the EPO and its Boards of Appeal described in Part III.A is particularly useful even to jurisdictions that are outside of the EPC.²³⁴ In fact, certain non-EPC legal regimes may offer national patent offices and courts even greater latitude to exclude patents covering medical treatments than does the EPC. For example, EPC Article 53(c), coupled with Article 54(5), creates an express carve-out for medical treatments that involve the application of a novel application of a known drug. But this carve-out does not exist in the TRIPS Agreement,²³⁵ and TRIPS member states that have elected to exclude patentability of medical treatments may do so unreservedly, without permitting patents on treatments that involve a drug.²³⁶

²³² See *id.* at 36 (explaining how T cells are removed from your body, modified, and then placed back in a patient’s body for the purpose of destroying cancer cells).

²³³ See **INDs Information**, *supra* note 31, at 1–2.

²³⁴ See discussion *supra* Part III.A.

²³⁵ See TRIPS Agreement art. 27, *supra* note 104.

²³⁶ See Michael H. Davis, Excluding Patentability of Therapeutic Methods, Including Methods Using Pharmaceuticals, for the Treatment of Humans Under Trade Related Aspects of Intellectual Property Rights Article 27(3)(A), 43 **Hofstra L. Rev.** 185, 185–86 (2014).

IV. IMPLICATIONS AND OUTLOOK

In Part III above we conclude that under the legal standards prevailing in Europe, the United States, and numerous other countries, CAR-T and other gene and cell therapies can be classified as medical treatments that are not subject to patent protection. In this Part, we examine the implications of this finding both for current practice and future developments.

A. Existing CAR-T Patents: Post-Grant Challenges

As noted in Part II.C above, numerous patents have been issued, and many more applications have been filed around the world, to protect CAR-T and other gene and cell therapies. If the analysis contained in Part III is correct, then many, if not all, of these patents are contrary to existing statutory exclusions of patentability under the EPC and similar statutory regimes.²³⁷ As such, it is likely that when the owners of such patents assert them in litigation, they would be subject to successful invalidity defenses by the alleged infringers.²³⁸

However, even if such patents could successfully be challenged in litigation, the existence of such patents “on the books,” even if invalid, can itself significantly impact private behavior and chill productive research and development of competing products. The situation is complicated further if medical treatment patents are included in larger patent portfolios that include both medical treatment patents as well as patents covering drugs or medical devices that are not barred by medical treatment patentability exclusions. For all of these reasons, there is a recognized public interest in clearing the market of invalid patents.²³⁹

There are several existing mechanisms by which patents may be challenged after grant. In Europe, issued patents may be challenged in an opposition proceeding under Article 99 of the EPC.²⁴⁰ Article 99 provides that “any person” may file an opposition seeking to invalidate an issued European patent within nine months of its publication in the European Patent Bulletin.²⁴¹ In addition to lack of disclosure and patents granted with a subject-matter that extends beyond the content of the application as filed, EPO oppositions can be filed when the patent is not patentable under Articles 52 to 57 of the EPC, which of course includes Article 53(c) regarding medical treatments.²⁴²

Issued patents may also be challenged in the United States using a number of procedures before the Patent Trial and Appeals Board (PTAB), including post-grant review (PGR)²⁴³ and inter partes review (IPR).²⁴⁴ However, neither PGR nor IPR proceedings are relevant vehicles for asserting the medical practitioner immunity granted under Section 287(c) of the Patent Act (as this

²³⁷ Guidelines for Examination in the European Patent Office, *supra* note 168, at Part G, ch. 2, § 4.2.1.

²³⁸ Id.

²³⁹ See *Lear, Inc. v. Adkins*, 395 U.S. 653, 670 (1969) (recognizing an “important public interest in permitting full and free competition in the use of ideas which are in reality a part of the public domain”).

²⁴⁰ EPC art. 99, *supra* note 93.

²⁴¹ Given the recent advent of CAR-T and other gene and cell therapies, we estimate that most patent applications covering these technologies are still being examined at the EPO, and in most cases, the nine-month deadline to file oppositions against prospective patents has not been triggered. Id.

²⁴² Id.

²⁴³ 35 U.S.C. § 321 (2017).

²⁴⁴ § 311.

immunity is a defense to a claim of infringement rather than a challenge to an asserted patent).²⁴⁵ Thus, in the United States, the only viable means for challenging the enforcement of medical treatment patents is likely to be an immunity defense under Section 287(c).

Traditionally in the United States, Europe, and elsewhere, only a patentee's direct competitors have had sufficient incentives to monitor and challenge patents in oppositions and other post-grant proceedings.²⁴⁶ However, recent years have seen the emergence of public watchdog entities such as Unified Patents that raise funding to challenge questionable patents in a range of technology markets (e.g., mobile devices, automotive technology, Internet of Things, etc.).²⁴⁷ Given that the cost of mounting an opposition or post-grant challenge to patents is significantly lower than the cost of patent litigation in general, it is possible that entities may emerge to challenge questionable patents in the gene and cell therapy sector as well, at least in Europe and other jurisdictions in which the validity of such patents is in doubt.²⁴⁸

B. Future Examination Guidance

Given the recent advances in CAR-T and other gene and cell therapies, patents covering these techniques are still relatively young. Thus, while there are comparatively few issued patents covering these techniques today, a large number of patent applications is likely pending in the examination process around the world, a number that is likely to increase over time. If such techniques are not eligible for patent protection under applicable statutory and judicial limitations on patentability of medical treatments, then it would be far more efficient for examining patent offices to deny the issuance of patents on such claims, rather than issuing such patents and waiting for them to be invalidated in adversarial proceedings such as oppositions and IPRs.

Yet surprisingly few patent offices have, to date, evidenced careful consideration of patentability limitations on such technologies, possibly because applicants have characterized them as products rather than medical treatments.²⁴⁹ Accordingly, the time is ripe for patent offices around the world to consider the patentability of CAR-T and other gene and cell therapies in view of national statutory and judicial limitations on the patentability of medical treatments. Such guidance is valuable both to individual patent examiners considering complex technical applications, as well as to the industry and patent bar.

Thus, we would recommend that the EPO move rapidly to publish definitive guidance regarding the patentability of CAR-T and other gene and cell therapies in the Guidelines for Examination, and that the USPTO do the same in its Manual of Patent Examination Procedures (MPEP). With leading patent offices issuing such guidance, patent offices in other jurisdictions will have the opportunity to consider the proper interpretation of their own laws and regulations in this area. The lack of such guidance, however, can have a contagious effect, as patent offices that unwittingly allow such applications in contravention of their own laws may then lead other patent

²⁴⁵ § 287.

²⁴⁶ See Susan J. Marsnik, *Will the America Invests Act Post-Grant Review Improve the Quality of Patents? A Comparison with the European Patent Office Opposition*, U. St. Thomas: Ethics & Bus. L. Faculty Publ'n (2012), <http://ir.stthomas.edu/ocbeblpub/25> (discussing empirical studies about what triggers opposition in the EPO and the United States and how the opposition creates a societal benefit by reducing the number of invalid patents).

²⁴⁷ See *What is Unified?*, *Unified Patents*, www.unifiedpatents.com.

²⁴⁸ Sapna Kumar, *Standing Against Bad Patents*, 32 *Berkley Tech. L.J.* 87, 91, 94 (2018).

²⁴⁹ See EMA, *Annex I: Summary of Product Characteristics*, *supra* note 213, at 2 (specifying that Kymriah is a product and listing it as such rather than referring to it as a medical treatment).

offices considering PCT applications for the same inventions to issue patents that are contrary to their own laws without due consideration.

C. Potential Statutory Amendments

If, as we contend, CAR-T and other gene and cell therapies are found in Europe and other jurisdictions not to be eligible for patent protection under existing statutory and judicial limitations on patenting medical treatments, then it is likely that a strong response from the biopharmaceutical industry will ensue. Such responses are not without precedent and have led, among other things, to legislative concessions including the 2000 amendments of the EPC,²⁵⁰ the Hatch-Waxman Act in the United States,²⁵¹ and numerous pro-industry concessions in TRIPS and other international trade agreements.²⁵² In fact, lobbying for legislative reform to counter or reverse unpopular statutory, regulatory or judicial rules is a common tactic across industries.

As recent negotiations over intellectual property in various bilateral and multilateral trade agreements have shown, legislatures in a number of countries have proven willing to make concessions in order to satisfy the demands of major trading partners such as the United States.²⁵³ Thus, it is not unlikely that some jurisdictions that currently have statutory or judicial limitations on the ability to patent medical treatments will, in the future, consider legislation designed to limit or overturn those limitations, at least with respect to CAR-T and other gene and cell therapies.

As these jurisdictions consider such legislation, we would urge them to recall the important countervailing considerations promoting public health and the unfettered ability of physicians to treat patients.

The biopharmaceutical industry is likely to oppose any formalized limitation on the ability to patent CAR-T and other gene and cell therapies with recourse to well-known arguments regarding the need to incentivize biomedical research and development (R&D) through patent-based exclusivity.²⁵⁴ This argument, which is not wholly without merit, posits that the exclusivity afforded by patents is necessary to enable drug and device developers to recoup their high costs of R&D, and that without the opportunity to charge monopoly rents during this exclusive period and block market entry by lower-priced competitors, developers would have little incentive to discover and develop new lifesaving drugs and devices.²⁵⁵

²⁵⁰ See *Sterckx & Cockbain*, *supra* note 95, at 62–66.

²⁵¹ 21 U.S.C. § 355(j) (2017).

²⁵² See, e.g., Ebenezer Tetteh, *Pharmaceutical Innovation, Fair Following and the Constrained Value of TRIPS Flexibilities*, 14 *J. World Intell. Prop.* 202, 208 (2011) (“OECD nations with ethical pharmaceutical firms have taken a pro-industry stance—and understandably so, given difficulties of balancing industrial policies, macroeconomic and health policy objectives—to impose TRIPS-plus conditions via bilateral and region-free trade arrangements.”).

²⁵³ See United States-Mexico-Canada Agreement, Sept. 30, 2018, ch. 20, *Off. U.S. Trade Representative*, <https://ustr.gov/trade-agreements/free-trade-agreements/united-states-mexico-canada-agreement/agreement-between>.

²⁵⁴ See Sara Parker-Lue et al., *The Ethics and Economics of Pharmaceutical Pricing*, 55 *Ann. Rev. Pharmacology & Toxicology* 191, 197 (2014).

²⁵⁵ Many of the assertions inherent in these arguments are contested. See, e.g., Vinay Prasad & Sham Mailankody, *Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval*, 177 *J. Am. Med. Ass’n Internal Med.* 1569, 1569–75 (2017); Parker-Lue et al., *supra* note 252, at 197; Marc-Andre Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 *PLoS Med.* 29, 29 (2008), <https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050001>.

Certainly, some ability to recoup R&D costs and avoid immediate competition from free riders is necessary for private sector pharmaceutical developers to remain viable. However, pricing in the pharmaceutical market today is not based on a cost-recovery model. Rather, pharmaceutical firms appear to develop pricing strategies based on what the market will bear, or the value that the market places on their products.²⁵⁶ This approach is nowhere more evident than in the field of gene and cell therapy. As discussed in the Introduction, CAR-T treatments such as Kymriah and Yescarta are priced at US\$475,000 and US\$373,000 per treatment, respectively.²⁵⁷ The upward trend in pricing of gene therapies is likely to continue, as indicated by Novartis's recent announcement that \$4-5 million per patient would be a "cost effective" price for a new gene therapy under development for spinal muscular atrophy (SMA).²⁵⁸

Yet the incremental cost of providing such treatments has been estimated by CAR-T pioneer Carl June to be in the range of \$15,000.²⁵⁹ Moreover, a significant portion of the R&D that contributed to the discovery of CAR-T and other gene and cell therapies can be attributed to basic research funded by government and philanthropic sources. For example, in the United States, through July 2017 the National Institutes of Health have funded 365 research projects involving chimeric antigen receptors amounting to US\$204 million in financial support.²⁶⁰ Of course, we acknowledge that basic scientific research, such as that funded by the federal government, is not sufficient to develop, test and bring a safe and efficacious therapeutic to market. Even conservative estimates place the fully-loaded cost of developing a new cancer therapy in the neighborhood of \$650 million,²⁶¹ with others estimating as high as \$2.7 billion.²⁶² Nevertheless, there is ample evidence that the high prices of today's gene therapies are based not on their cost of development or production, but on the price that the market will bear.²⁶³

²⁵⁶ See Richard G. Frank & Paul B. Ginsburg, Pharmaceutical Industry Profits and Research and Development, *Health Affairs*, Nov. 12, 2017.

²⁵⁷ See Kolata, supra note 2; Beasley, supra note 8.

²⁵⁸ Miller, supra note 10.

²⁵⁹ Final Meeting Summary of the 8th Cell Therapy/FDA Liaison Meeting, Int'l Soc'y for Cellular Therapy (2018), https://cdn.ymaws.com/www.celltherapysociety.org/resource/resmgr/files/PDF/Meetings/CTLM/October_2008/October_17_2008_Cell_Therapy_Liaison_Meeting_Summary_FINAL.pdf ("Dr. June reviewed their approach to adoptive T cell therapy and clinical scale expansion which costs in excess of \$15,000 per patient."); Donald B. Kohn et al., CARs on Track in the Clinic, 19 *Molecular Therapy* 432, 436 (2010) ("With respect to financial considerations, Steven Rosenberg estimated that the full costs at the NCI Surgery Branch to produce and release an autologous gene-engineered T-cell product, including all laboratory supplies and reagents, staff salaries, and product certification assays, amount to about \$15,000 per treated patient (others suggested somewhat higher costs per patient, in the range of \$20,000 to \$25,000, in part based on differing costs for vector production and qualification). These costs do not cover capital depreciation, overhead, and rental costs; however, the estimates compare favorably with the procurement costs for unrelated allogeneic stem cell products for clinical transplantation.").

²⁶⁰ James Love, Federal Funding to Organizations for Projects Related to Chimeric Antigen Receptors, *Knowledge Ecology Int'l* (July 25, 2017), <https://www.keionline.org/23838> (basing the number of projects on a study of the NIH RePorter database as of July 2017).

²⁶¹ Prasad & Mailankody, supra note 274.

²⁶² DiMasi JA, Grabowski HG & Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs, 47 *J Health Econ*. 20 (2016).

²⁶³ For example, Pascal Touchon, Senior Vice President of Novartis Oncology, has publicly stated that "When we considered the price of tisagenlecleucel [Kymriah] in the United States, the first thing we looked at was its medical value and the value it brings to patients . . . Then we looked at the value to the health-care system and society." Jo Cavallo, Weighing the Cost and Value of CAR T-Cell Therapy, *ASCO Post* (May 25, 2018), <http://www.ascopost.com/issues/may-25-2018/weighing-the-cost-and-value-of-car-t-cell-therapy/>.

At price levels such as these, lifesaving gene and cell therapies may be unaffordable to many, including both uninsured and underinsured individuals in private insurance jurisdictions such as the United States, and to large swaths of the population in subsidized and national healthcare systems. Although patents are not, in themselves, the causes of exorbitant pricing for CAR-T and other gene and cell therapies, patents enable developers to charge any price that the relevant market will bear. Governments that face the decision of whether to allow patents on gene therapies or not should always put monopolies, rather than patients, at risk. Giving the fact that the business model of private sector pharmaceutical developers relies, at least in part, on obtaining these patents, we recognize that fully exercising this patentability exclusion could lead to a broader debate on how to induce private investments in these new therapies. While that debate falls outside the scope of this paper, we believe that the discussion should be based on alternative mechanisms for inducing innovation, such as progressive delinkage, and not about eliminating limitations on patentable subject matter to include gene therapies.²⁶⁴

CONCLUSIONS

More than eighty countries, including the members of the European Patent Convention, the United States, Canada, New Zealand, China, Japan, and India, currently exclude or limit the patentability of methods of medical treatment. CAR-T and other recent gene and cell therapies, which operate based on the extraction of genetic or cellular material from a patient, the alteration of such material, and the reintroduction of such material to the patient's body, have been characterized by their developers as products. Yet this characterization is largely a fiction. These therapies are more akin to medical treatments such dialysis than manufactured products and should thus, under most or all of these legal regimes, be excluded from patentability, or be subject to limited patent enforcement. Accordingly, we urge national patent offices to update their examination procedures and practices to take these patentability limitations into account and to publish guidance clearly explaining this approach to applicants.

²⁶⁴ Delinkage “describes the idea that temporary monopolies and the associated high drug prices should not be used to fund pharmaceutical research and development, as well as a set of policy proposals that would replace monopolies and high prices with alternative incentives based upon cash rewards, and expanded funding for research, drug development, and clinical trials through a combination of grants, contracts, tax credits, and other subsidies.” Progressive de-linkage means that governments implement reforms over time that sequentially and progressively move prices closer and closer to affordable generic prices, and reform incentives so they no longer rely upon high prices. See What is Delinkage?, **Delinkage.org** (Feb. 28, 2016), <https://delinkage.org/overview/>.

APPENDIX A

International Trade Agreements Including Exclusion of Medical Treatment Patents

Canada – Korea (article 16.12)
China – Korea (article 15.15)
Colombia – EFTA (article 6.9)
EU – CARIFORUM (article 148)
Japan – Switzerland (article 117)
Korea – Australia (article 13.8)
Korea – Vietnam (article 12.7)
NAFTA 1992 (article 1709)
Peru – EFTA (article 6.9)
Switzerland – China (article 11.8)
USA – Australia (article 17.9)
USA – Bahrain (article 14.8)
USA – Jordan (article 4.18)
USA – Oman (article 15.8)
US–DR–CAFTA (article 15.9)
US – Colombia (article 16.9)
US – Peru (article 16.9)
TPP/CPTPP (article 18.37)
USMCA (article 20.36.3(b))

APPENDIX B

Countries Implementing Exclusion for Medical Treatment Patents in National Legislation

Argentina: Article 6(e) of Law 24.481 enacted on March 1995

Albania: Article 6.4 of Law No. 9947 enacted on July 7, 2008 as amended up to Law No. 55/2014 of May 29, 2014

Andean Community: Article 20(d) of Decision No. 486 Establishing the Common Industrial Property Regime, adopted on September 13, 2000

Bahrain: Article 3(d) of Law No. 1 of 2004 on Patents and Utility Models, enacted up to January 23, 2004

Barbados: Article 11(c) of the Patents Act 2001, enacted July 25, 2001 as amended by Act No. 2 of 2006

Belgium: Section 7.2 of the Patent Law of March 28, 1984, as amended up to December 22, 2008

Brunei Darussalam: Section 16 of the new Patents Act (2011)

China: Article 25 of the Patent Law

Chile: Article 37(d) of Law No. 19.039 on Industrial Property, consolidated text as of February 6, 2012

Costa Rica: Article 1.4(b) of Law 6867 enacted on April 1983 and last amended on November 2008

Croatia: Article 6.3 of the Patent Act, enacted on October 14, 2003

Ecuador: Article 273.2 of the Organic Code on the Social Economy of Knowledge, Creativity and Innovation, enacted on November 30, 2016

Egypt: Article 2.3 of the Law No. 82 of 2002 on the Protection of Intellectual Property Rights, enacted on June 1, 2002

El Salvador: Article 107(c) Law on Intellectual Property enacted on July 14, 1993, as amended up to Legislative Decree No. 611 of February 15, 2017

Estonia: Section 7.2 of the Patents Act enacted on March 15, 1994, consolidated text of January 1, 2015

European Union: Article 53(c) of the European Patent Convention (16th edition) published on June 2016

France: Article L611-16 of the Intellectual Property Code enacted on June 30, 1992, consolidated version of March 17, 2017

Georgia: Article 17(b) of the Law No. 1791 enacted on February 5, 1999, as amended up to Law No. 3031 of May 4, 2010

Germany: Section 2(a)1 of the Patent Act, as amended up to Act of October 8, 2017

Ghana: Section 2(c) of the Patent Act 2003 enacted on December 30, 2003

- Guatemala: Article 92(a) of the Industrial Property Law enacted on September 17, 2000
- Honduras: Article 5.9 of the Industrial Property Law enacted on December 29, 1999
- Iceland: Article 1 of the Patents Act No. 17/1991, as amended up to Act No. 126/2011
- India: Article 3(i) of the Patents Act enacted on September 1970 and as amended up to April 2005
- Indonesia: Article 7 of the Law of the Republic of Indonesia No. 13 on Patents enacted on July 28, 2016
- Israel: Article 7 of the Patent Law, 5727-1967, consolidated version of 2014
- Jordan: Article 4(c) of the Law No. 32 of 1999 on Patents, enacted on September 19, 1999
- Kenya: Article 21.3(c) of the Industrial Property Act 2001 (Act No. 3 of 2001), as amended up to Act No. 11 of 2017
- Lebanon: Article 3.3 of the Law No. 240/2000 of 2000 on Patents, enacted on August 6, 2000
- Lithuania: Article 2 of the Law No. I-372 of January 18, 1994, on Patents, as amended by Law No. X-1119 of May 10, 2007
- Malaysia: Article 13(d) of the Patents Act 1983, enacted on 1983 as amended up to August 2006
- Malta: Article 4.4 of the Patents and Designs Act (Chapter 417), enacted on May 31, 2002
- Mauritius: Article 11.3(c) of the Patents, Industrial Designs and Trademarks Act 2002 enacted on July 1, 2002
- Mexico: Article Art. 19.VII of the Industrial Property law enacted on June 1991, consolidated text published in the Official Journal of the Federation on March 13, 2018
- Montenegro: Article 7.2 of the Law on Patents enacted on July 15, 2015
- Morocco: Article 24(b) of Law No. 17-97 on the Protection of Industrial Property enacted on February 14, 2000, as amended by Laws No. 31-05 and No. 23
- New Zealand: Article 16.2 of the Patents Act 2013 enacted on September 12, 2013
- Nicaragua: Article 7(b) of Law on Patents, Utility Models and Industrial Designs (No. 354 of 2000) enacted on May 31, 2000
- Norway: Section 1 of the Patents Act No. 9 enacted on December 15, 1967, consolidated text of 2018
- Panama: Article 14.7 of Law No. 35 enacted on May 10, 1996, on Industrial Property
- Papua New Guinea: Section 2 of the Patents and Industrial Designs Act 2000 enacted on June 30, 2000
- Paraguay: Article 4(e) of Law No. 1.630/2000 on Patents, as last amended by Law No. 2.593/2005
- Philippines: Section 22.3 of the Intellectual Property Code of the Philippines (Republic Act No. 8293)

Poland: Article 29(iii) of the Industrial Property Act of June 30, 2000, as amended up to Act of July 24, 2015

Portugal: Article 53.3(c) of the Industrial Property Code, as amended up to Law No. 46/2011 of June 24, 2011

Romania: Article 8(d) of Law No. 64/1991 on Patents (as amended up to Law No. 83/2014)

Serbia: Article 9.2 of the Law on Patents No. 99/2011, enacted on December 25, 2011

Singapore: Section 16(2) of the Patents Act (No. 24 of 2001), as amended by Act No. 2 of 2007

Slovakia: Article 6.1(c) of the Act No. 435/2001 Coll., consolidated version of 2009

Spain: Article 5.4 of the Law No. 24/2015 of July 24, 2015, on Patents

Sweden: Article 1 of the Act (2004:159) Amending the Patents Act (1967:837)

Switzerland: Article 2 of the Federal Act of June 25, 1954, on Patents for Inventions, as amended up to January 1, 2017

Thailand: Article 9.4 of the Patent Act B.E. 2522 (1979), as amended up to December 31, 1998

FYR Macedonia: Article 26 of the Law on Industrial Property enacted on January 11, 2009

Seychelles: 6.1(e) of the Industrial Property Act 2014 enacted on April 15, 2014

Trinidad and Tobago: Article 12.1(d) of the Patents Act, 1996 enacted on December 31, 1995

Tunisia: Article 2(d) of the Law No. 2000-84 of August 24, 2000, on Patents

United Kingdom: Article 4A of the Patents Act 1977, as amended by the Patents Act 2004

Uganda: Article 8.3(c) of the Industrial Property Act, 2014, enacted on January 5, 2014

Uruguay: Article 14(a) of Law No. 17.164 of September 2, 1999, regulating Rights and Obligations relating to Patents, Utility Models and Industrial Designs

Vietnam: Article 59.7 of the Law No. 50/2005/QH11 enacted on November 29, 2005, on Intellectual Property

Zambia: Article 17(a) of the Patents Act 2016